Lung cancer in Scotland : past, present and future

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I hereby declare the that the research contained within in this thesis was conducted by myself

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Abstract

Aims: Lung cancer survival in Scotland appears to be inferior to that in many other countries, and it has been proposed that this is due to low use of treatment. To investigate if this is indeed the case and to understand how outcomes might be improved a series of studies were conducted

Methods and Materials: A systematic review of data published on lung cancer treatment and survival rates was performed. Then, two cohorts of patients diagnosed with lung cancer in 1995, one from British Columbia (BC) and a second from Scotland, were compared to investigate differences in patient and tumour characteristics, factors affecting treatment, and survival. To assess the impact of recent changes in cancer care in South-East Scotland (SCAN) comparison was made with a 2002 cohort. Finally, models were developed to investigate the gap between optimal and actual treatment.

Results: Comparison of data from 2073 BC and 3833 Scottish patients demonstrated that fewer Scottish patients had pathological diagnosis, and more cases regional-stage disease. The adjusted odds for receiving any treatment was 0.7(0.6-0.8) Scotland v BC, and 0.4 (0.3-0.5) for potentially curative therapy. Five-year relative survival rate was 12% in BC and 6% Scotland ($p<0.001$). The adjusted hazard of death Scotland v BC following surgery was 1.3(1.1-1.6), radiotherapy 1.5(1.4-1.6) and chemotherapy 1.5(1.3-1.5). Data of 927 patients from SCAN diagnosed in 1995 were compared with that from 971 diagnosed in 2002. The surgical rate was unchanged at 11%, but the use of radical radiotherapy trebled, and chemotherapy for non-small cell lung cancer doubled. Overall survival at two-years increased from 11% to 15% (log rank $p= 0.003$) with hazard of death 0.7 (0.6-0.8) 2002 v 1995. The models suggested that based on stage distribution, performance status and co-morbidity the use of surgery was close to optimal, but radiotherapy and chemotherapy were possibly under utilised. Optimal use of treatment would increase long term survival slightly, but not sufficiently to bring survival rates in-line with that observed in Canada.

Conclusions: Survival of Scottish lung cancer patients was inferior to in BC, but the reasons are more complex than just under-treatment.

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Glossary of terms and abbreviations

ANOVA – analysis of variance

BC – British Columbia

BCCA – British Columbia Cancer Agency

CDN$ - Canadian dollars (£1 approximately = CDN$ 1.3)

Chemo - chemotherapy

E-SCLC – extensive stage small cell lung cancer

EUROCARE – a collaboration of European Cancer Registries

L-SCLC – limited stage small cell lung cancer

Mets – metastases

MSP – Medical Services Plan – the Canadian healthcare scheme

NHS – National Health Service – the British healthcare scheme

NOSCAN – North of Scotland Cancer Network

NSCLC-NOS – non small cell lung cancer not otherwise specified

PCT – potentially curative therapy

PORT – post-operative radiotherapy

RT – radiotherapy

SCAN – South East Scotland Cancer Network

TNM – tumour, node, metastases staging system for cancer

WOSCAN – West of Scotland Cancer Network

Chapter 1

Introduction: History, aetiology and treatment of lung cancer

1) History and aetiology of lung cancer

'This is the only case of cancer of the lung which I have ever met with; so that I presume that the disease rarely attacks this organ'

1849. John Hughes Bennett, Professor of Pathology, University of Edinburgh.

Lung cancer is a modern disease. In 1881, Fraser was unable to present more than a single case to the Medico-Chircurgical Society of Edinburgh [145]. The number of cases of lung cancer in Scotland rose dramatically throughout the first half of the 20th century and by the end of the 1950s, when the first national figures became available, there was an average of 2078 cases per annum in men and 350 in women [175]. The incidence continued to rise, peaking in the mid-1980s, with around 3300 cases per annum in men and 1300 in women. Recently, the number of cases occurring in men has declined, but the incidence in women is still rising. In 2002, there were 2600 men and 2000 women with lung cancer in Scotland [98]. Currently the lifetime risk of lung cancer in Scottish men is 1 in 11, and 1 in 17 for women [98].

What is the cause of this epidemic? In the early days many causes were suggested including syphilis, tuberculosis, cobalt, tar, and car exhaust fumes, but the potential link to tobacco was not confirmed till the mid 20th century. In 1950, Wilder and Graham published their paper in Journal of American Medical Association 'Tobacco as a possible etiological factor in bronchogenic carcinoma' [210]. Then, in the same year Doll and Hill published their

landmark study in which they found that in a case-series of over 1300 men with lung cancer, 99.5% were smokers [54].

Tobacco was first imported to Europe from the Americas in the mid 16th century and was soon promoted by the medical profession as a 'cure-all'. John Gerard the English herbalist thought it cured '*migraine, toothache, gout, ulcers, asthma and deafness*'. [45] However, even at this time tobacco had its critics including King James VI of Scotland who in 1604, described tobacco as '*a custome loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs*'. However, it was not until 1761 that the possible link with tumours was noted by Sir John Hill in his *'Cautions against the immoderate use of snuff'*.

Despite these observations smoking became increasingly popular, but did not become widespread until the 1880s with the invention of machinery to mass-produce cigarettes. In the First World War free cigarettes were distributed to the troops in the trenches, and by the 1920's more than half the male population in the United Kingdom smoked. This rose further during the Depression and the Second World War and by the 1940's it is estimated that more than 80% of men smoked. Smoking did not become socially acceptable for women until the Second World War, and therefore the peak rate of female smoking was much later; around the early 1960's. This accounts for the temporal differences in the incidence of lung cancer between men and women over the last century [175].The generation of men born around 1904 and women born around 1920 had the highest life-time risk of lung cancer.

Since the publication of the results of the work by Doll *et al* in 1950 and the publicity associated with these findings, the rate of smoking in Scotland has slowly declined. At present it is estimated that around 30% of Scots smoke [141]. It is hoped that this figure will decrease further with the ban of smoking in public places, as stopping smoking can reduce the risk of developing lung cancer. In a recent re-analysis of the 1950's cohort of doctors, although lifelong smokers were 15 times more likely to develop lung cancer than non-smokers, those that gave up by age 64 were 7.5 times more likely to develop lung cancer than non-smokers, those that gave up at age 54 were 3.8 times, and age 44 were 2.0 times more likely [55].

Though the public health message about smoking seems to be increasingly effective in Northern Europe and North America, smoking is becoming more prevalent in Eastern Europe and many other developing countries. Currently the highest incidence of lung cancer in the world is in the new European Union countries, notably Poland, the Czech Republic and Hungary [196].

Other aetiological factors in the development of lung cancer

It is estimated that smoking (either personal or passive) accounts for around 90-95% of lung cancer but there are other aetiological factors[2].

1) Occupational exposures – These include tar and coal (contains carcinogenic benzo(a)pyrene) and heavy metals, such as arsenic, cadmium and nickel. Whether or not

diesel fumes and exposure to silica are associated with an increased the risk of lung cancer remains controversial [3]

2) Asbestos – Asbestos, either alone or synergistically with cigarette exposure, has been shown to be associated with a higher incidence of lung cancer [86]

3) Radiation – Either come from i) naturally occurring sources such as radon, or ii) exposure medical X-rays and gamma rays either for diagnosis or treatment.

i) Radon gas is released from the rocks in certain parts of the world, for example Aberdeenshire in Scotland. The association of radon gas and lung cancer was first noticed in miners [157]. Whether or not exposure to radon in homes is linked to increased risk of lung cancer remained controversial, but in 2006 an analysis that included data on over 9000 people was published and concluded that there was an excess risk of 0.1 per Bq/m^3 radon levels in houses [109].

ii) The risk of exposure to diagnostic medical X-rays remains controversial; studies from patients screened for tuberculosis suggested there was an increased risk of lung cancer [47]. However, recently the level of risk of medical radiation has been questioned and a hypothesis that low doses of radiation may in fact be protective against cancer has been proposed, but this remains controversial [204]. Exposure to therapeutic radiation to the chest is undoubtedly associated with an increased risk of lung cancer, for example mediastinal radiotherapy for Hodgkin's lymphoma, especially if the patient continues to smoke [200].

4) Air pollution - the role of air pollution in the development of lung cancer is difficult to establish due to the close linkage of other factors, such as smoking, which are also associated with urban areas. A recent analysis from six US cities suggested there maybe a link between increased levels of particles in the air and lung cancer [110].

The history of the treatment of lung cancer

1) Surgery

In 1912 the first lung cancer resection, a lobectomy, was performed in London by Davies, but the patient died a few days later of post-operative complications [131]. The main difficulty was anaesthesia; in order to maintain adequate oxygenation during the operation the lung had to be kept inflated during the procedure, which impaired surgical access. However, developments in anaesthetic techniques during the 1920's enabled the first pneumonectomy to be successfully performed in 1933 by Ewart Graham in New York [80].

In the early years of lung cancer surgery the post-operative mortality was around 50%. However, new trauma surgery techniques developed during the Second World War led to a significant reduction in the post-operative mortality, such that by the mid 1950's lung cancer resections had become commonplace. Further improvements in surgical techniques, anaesthesia and post-operative care mean that today the overall post-operative mortality rate is between 2 and 4% [4, 17, 46].

The first two publications reporting long term survival following lung cancer surgery performed in the late 1940s and early 1950's demonstrated a 20% five-year survival rate [144, 184].

Today most surgical series quote five year survival rates of around 40-45% [19, 69], and up to 60% for patients with stage 1 disease [207].

2) Radiotherapy

Radiotherapy was first used in the treatment of inoperable lung cancer in the 1920s when radium seeds were inserted into the tumour using a bronchoscope [137]. In the years following the Second World War the development of radiotherapy machines that could deliver high-energy X-rays beams enabled much higher doses to be delivered to the lung without excessive toxicity. The first case reports of patients cured of lung cancer with radiotherapy were published in the early 1950s. One series of 624 patients, referred between 1944 and 1948 to the Brompton Hospital in London, included 109 who received radiotherapy to a dose of 4000rads (40Gy) [28]. For this group of patients the two-year survival rate was 15.5%, and at five years 5.9% were still alive.

The first Scottish case-series of lung cancer patients treated with radical radiotherapy was published in 1989 from the Edinburgh Cancer Centre [143]. It included data on 446 patients treated between 1974 and 1981. All received 20 fractions of radiotherapy which was planned using chest radiographs and a barium swallow to identify involved lymph nodes. The five-year survival for the group as a whole was 10.6%. Those patients without obvious nodal involvement had a five-year survival of 18.6%, compared with 7.4% for those with nodal enlargement.

Since the publication of this series there have been many changes in the management of lung cancer. One major change has been the introduction of CT scanning during the 1980s and 1990s. This diagnostic tool is more accurately able to identify metastatic spread to lymph nodes and distant sites. Therefore, some of the improvement in the survival of patients with early stage disease observed during this period can simply be attributed to the use of more accurate staging, the so called 'Will Rogers' effect [63].

CT scanning is now also used in the planning of radiotherapy; enhancing the accuracy of tumour localisation and dose calculations. Today, 3-D conformal radiotherapy, where the treatment volume is shaped to encompass the tumour and minimise the dose to normal tissues, is the standard of care. However, even with these advances the results remain disappointing with three-year progression-free survival below 30% [111].

3) Chemotherapy

The first reports of the response of lung cancer to nitrogen mustard chemotherapy were published in the early 1950s [28]. In the Brompton Hospital case series published in 1951, 54 patients were treated with chemotherapy alone, using mainly nitrogen mustard. About half had symptomatic benefit, but almost all suffered chemotherapy induced vomiting, and many refused to have further treatment. Complete responses were observed in a number of patients with small-cell lung cancer (SCLC), which sparked great interest [28].

Over the next two decades, with the introduction of new chemotherapy drugs, such as cyclophosphomide and cisplatin, and better anti-sickness agents, the use of chemotherapy in the treatment of SCLC became commonplace. By the late 1970s and early 1980s case-series and clinical trials confirmed that patients could experience long term survival with chemotherapy for SCLC [87].

However, it was not until the mid-1990s that the use of chemotherapy for patients with non-small cell lung cancer (NSCLC) became widely accepted. With a much lower response rate, critics felt that the toxicity was not worth the small survival benefit. However, in 1995 a meta-analysis of chemotherapy for NSCLC was published in the British Medical Journal [6] and demonstrated in the palliative setting a 10% absolute improvement in survival at one-year, and when combined with radical radiotherapy there was an additional 4% improvement in survival at two years.

More recently, trials have been published which demonstrate that there is also a survival benefit when chemotherapy is used in the adjuvant setting after surgery for early stage NSCLC [56, 207].

2) Current recommended management of lung cancer

Lung cancer is not one disease, but a number of different pathological entities. For simplicity these are grouped into 'small-cell lung cancer' (SCLC), which is managed primarily with chemotherapy and 'non-small cell lung cancer' (NSCLC) a collection of different pathological types (mainly squamous cell, adenocarcinoma and large cell) that traditionally were managed mainly with surgery and radiotherapy.

Currently lung cancer is only curable when it is confined to the thorax, so the stage of the lung cancer at presentation is the primary determinant of treatment and prognosis. The current staging system for NSCLC is shown in Table 1.2a and 1.2b and SCLC in Table 1.3 [133, 138]

Table 1.2a TNM system for NSCLC (1997)

T1	3 cm surrounded by lung or visceral pleura, no evidence of invasion of proximal bronchus
T2	> 3 cm, or invading visceral pleura or causing atelectasis of the lobe, or involving proximal bronchus but >2cm from carina.
T3	Invading chest wall, diaphragm, mediastinal pleura, or pericardium, or lesion < 2 cm from carina or causing atelectasis of whole lung
T4	Invading mediastinum or involving heart, great vessels, trachea, oesophagus, vertebral body, or satellite nodules within same lobe or malignant pleural or pericardial effusion
N1	metastases in peribronchial or hilar lymph nodes.
N2	metastases in subcarinal or ipsi-lateral mediastinal lymph nodes.
N3	metastases in contra-lateral mediastinal or hilar lymph nodes, any supraclavicular lymph nodes.
M1	distant metastases.

Table 1.2b Staging system for NSCLC (1997)

Stage I	T1N0M0, T2N0M0
Stage II	T1N1M0, T2N1M0, T3N0M0
Stage III	T1N2-3M0, T2 N2-3M0, T3N1-3M0, T4N0-3M0
Stage IV	T1-4 N0-3 M1

Table 1.3 Staging for SCLC (Veterans Administration Lung Cancer Study Group)

Limited (L-SCLC)	Disease can be encompassed in a 'tolerable' radiotherapy field*
Extensive (E-SCLC)	Disease that cannot be included in the above definition

*Debate remains about patients with contra-lateral supra-clavicular lymph nodes or pleural effusions; these were included within the original definition of 'limited', but are frequently excluded from clinical trials.

A patient's general fitness is also a major determinant of treatment selection and prognosis. The WHO (Zubrod) performance status scale is probably the most widely used in lung cancer and is shown in Table 1.4.

Table 1.4 Performance status

WHO performance status	
0	Able to carry on normal activities without restriction
1	Symptoms but able to do light work
2	Marked restriction of activity but spends <50% time in chair/bed
3	Marked restriction of activity but spends more than 50% time in chair/bed
4	Unable to get out of bed

Current recommended treatment of lung cancer

In 2005, two systematic reviews of the literature relating to diagnosis, staging and management of lung cancer were published in the UK; one performed by the Scottish Intercollegiate Guidelines Network (SIGN) and the second by National Institute for Health and Clinical Excellence (NICE). The recommendations are summarised below:

Diagnosis and staging

- All patients with known or suspected lung cancer should undergo a contrast enhanced CT scan of thorax, liver and adrenal glands
- Bronchoscopy should be performed in patients with central lesions to obtain pathological specimen
- Percutaneous biopsy should be performed in patients with peripheral lesions
- A positron emission tomography (PET) scan should be performed in patients with a solitary pulmonary nodule where a biopsy is not possible
- PET scan should be performed in patients with NSCLC who are being considered for surgery or radical radiotherapy

Treatment of NSCLC

- All patients with Stage I and II, who are medically fit and who have adequate pulmonary function, should be offered surgery
- Adjuvant post-operative chemotherapy should be discussed with patients with pathological T2N0M0 or more advanced stage disease
- Post-operative radiotherapy should be considered after an incomplete excision

- Patients with Stage I or II with reasonable performance status who are not fit for surgery, or who decline it, should be offered radical radiotherapy
- Patients with Stage III with a good performance status should be offered radical radiotherapy with chemotherapy, provided the disease can be encompassed safely within a radical radiotherapy volume.
- Chemotherapy should be offered to patients with Stage III and IV disease with good performance status.
- Palliative thoracic radiotherapy should be offered to patients with advanced disease who have cough, haemoptysis or chest pain
- Palliative radiotherapy should be considered for patients with symptomatic brain metastases
- Palliative radiotherapy should be offered to patients with symptomatic bone metastases

Treatment of SCLC

- All patients should be offered platinum based multi-drug chemotherapy
- All patients with limited stage disease should be offered thoracic radiotherapy and, if there is a response to chemotherapy, prophylactic cranial irradiation
- Patients with extensive stage disease who have had a complete response at distant sites should undergo consolidation thoracic radiotherapy
- Palliative thoracic radiotherapy should be offered to patients with advanced disease who have cough, haemoptysis or chest pain

- Palliative radiotherapy should be considered for patients with symptomatic brain metastases
- Palliative radiotherapy should be offered to patients with symptomatic bone metastases

3) Previous research on lung cancer treatment and outcomes in Scotland

Over the past 25 years a number of studies have been published which examine the treatment and survival of lung cancer in Scotland. The Scottish Cancer Registry which has complete coverage of the country and high case ascertainment has aided this research.

The first prospective regional audit included data on patients resident in South East Scotland who were diagnosed with lung cancer in 1991 [64]. The records of 662 of the 1073 patients (63%) in the Scottish Cancer Registry were examined. 510 (82% of identified cases / 48% all cases in Scottish Cancer Registry from the region) had pathological confirmation, 441 (71%/41%) underwent bronchoscopy, and 112 (18%/10%) a CT scan. 130 (21%/12%) patients underwent surgery, 168 (27%/16%) radiotherapy (10 radical radiotherapy) and 69 (11%/6.5%) chemotherapy, including 61 of 125 (49%) patients with SCLC. The median survival for the whole cohort was 6 months, with 15% alive at 24 months. Of those treated with curative intent the median survival was 18 months, with 40% alive at two years.

In another study, a random sample of 262 of 1142 cases diagnosed in Glasgow in 1991-92 was examined to look at patterns of care [106]. Of this selected cohort, 78% underwent bronchoscopy and 36% a CT scan. Pathological confirmation was obtained in 69% of cases. Surgery was used in 5% of patients, radical radiotherapy 2.5% and 10.2% chemotherapy. 9% of the cases were alive at 3-years.

In a study conducted in Northern Scotland, Campbell *et al* identified a cohort of 661 patients diagnosed with lung cancer in 1995-1996, of whom 13% underwent surgery, 63% radiotherapy and 19% chemotherapy within the first year of diagnosis [31, 32]. Chemotherapy was less likely to be delivered to patients from socially deprived areas.

In 1998, a national retrospective audit of Scottish lung cancer patients diagnosed in 1995 was performed. The medical records of 3855 of the eligible 4225 cases (91%) were examined. The general results were published in 2001 [83] and showed a resection rate of 10.6%, a radiotherapy utilisation rate of 35.8% and chemotherapy of 16.2%, within six months of diagnosis. The median survival was 3.6 months, with 10% alive at two years. Patients who saw a respiratory physician had reduced hazard of death even when age, gender, deprivation, stage and pathology were taken into account [65]. A more detailed analysis of factors affecting the use of thoracic radiotherapy was published in 2002 [62] and showed age, extent of disease, involvement of a lung cancer specialist, pathological confirmation, and healthboard area all affected whether or not a patient received radiotherapy. However, detailed analyses of the factors affecting the use of surgery and chemotherapy have never been published.

Comparison of Scotland with other countries

EUROCARE is a collaborative effort of the European Cancer Registries and has published three reports (EUROCARE 1 1972-1984, EUROCARE II 1985-1989 AND EUROCARE III 1990-1994) [100, 167] comparing the survival for various cancers across Europe. In each of the three reports the survival rates for lung cancer patients in Scotland were below the European average. Therefore, to determine why Scottish lung cancer patients have inferior survival, and to ascertain if this is due to differences in patient and tumour characteristics and/or in treatment, a detailed comparison to a country with good lung cancer outcomes is required.

To date, there has been only one population-based international comparison examining factors that might explain the differences in lung cancer survival between countries [187]. This study examined impact of pathological type and stage distribution between Denmark, Norway and Finland to see if these factors could explain the lower lung cancer survival in Denmark. There were more patients with non-localised disease were found in Denmark, which was given as a possible explanation. However, the study did not include data on the treatment utilisation in the three countries, which obviously could have had an impact on outcome.

4) Rationale of this thesis

British Columbia (BC) is a province in Western Canada with a population of 4 million, half of whom live in the metropolitan area of Greater Vancouver, with the remaining population widely dispersed over nearly 1,000,000 square kilometers. All individuals resident in BC have access to free health-care through the Medical Services Plan. The British Columbia Cancer Agency (BCCA) provides cancer care to all patients in BC through its centres in Vancouver, Victoria, Kelowna and Fraser Valley. All the patients are treated with the assistance of unified management guidelines, which are available to all hospital and community doctors in BC. Linked with the BCCA is the British Columbia Cancer Registry, which has an estimated 93.5% case ascertainment, for all cancers combined. However, it is likely that the case ascertainment for lung cancer exceeds this, as lung cancer cases can be identified from surgical pathology reports, BCCA database or death certificates. The computerized records of BCCA detailing all cancer treatments are directly linked to the Cancer Registry.

Scotland has a similar population and healthcare system. The population is 5.5 million, the majority of whom live in the urban areas around Glasgow and Edinburgh and like BC, all patients have access to free healthcare through the National Health Service. There are five Cancer Centres, which function independently, in Glasgow, Edinburgh, Dundee, Aberdeen and Inverness. The Scottish Cancer Registry has a long association with these Cancer Centres and achieves nearly 97% case ascertainment for all cancer sites [26], but as in BC, the case ascertainment for lung cancer is likely to be higher than this.

Past

For patients diagnosed with lung cancer in British Columbia in 1992 the five-year relative survival rate for men with lung cancer was 12%, and 15% for women [34]. This compares with 6% for men and for women in Scotland for the period 1992-1996 [97]. Consequently, a comparison of lung cancer cases diagnosed in British Columbia and Scotland in 1995 has the potential to provide valuable information that could assist our understanding of why the survival in Scotland is inferior, and to inform on methods in which lung cancer management could be altered to improve the outcome of Scottish patients.

Present

Since the 1995 audit, in an effort to improve the survival, many changes have been made to the organisation of cancer services in Scotland. These changes have included the development of the Scottish National Guidelines [SIGN], the introduction of regional cancer networks and multi-disciplinary meetings, and the appointment of more lung cancer specialists. Therefore if recommendations on future changes to lung cancer services are to be made, it is important that data on more recent patient management and outcomes are also examined.

Future

Finally, though changes have been made to healthcare organisation, it is important to examine the gap between optimal and actual patient management. If patients are to receive the appropriate treatment it is important that the resources are in place to meet this demand. As noted above, the tumour type, stage at presentation, and the patient's performance status

are the primary determinants of the most appropriate treatment. If these factors are known within a population then the resources required for optimal cancer management can be estimated and future healthcare provision planned to meet the predicted demand.

Therefore, the aim of this thesis is to test the hypothesis that 'the outcome of lung cancer in Scotland is poor and that this could be improved by optimal use of treatment'.

To investigate this, a series of studies were performed

1. In order to contextualise the situation in Scotland, a systematic review was conducted to establish how treatment utilisation and survival rates vary around the world.

2. The characteristics of a population of Scottish lung cancer patients from 1995 were examined to establish whether the levels of treatment were sub-optimal and survival was poor

3. Comparison was made with a similar population from British Columbia diagnosed with lung cancer in the same year, to understand the differences in patient, tumour and management characteristics that might account for any differences in outcome.

4. A cohort of lung cancer patients diagnosed in 2002 from South-East Scotland was then compared with the patients from the same area diagnosed in 1995, to establish whether the changes in health service organisation have had any impact on use of treatment and survival

5. Finally, models were developed to investigate the potential gap between actual and optimal treatment.

CHAPTER 2

Comparison of international series examining treatment and survival of lung cancer patients

Factors affecting population-based cancer survival rates

The outcome of any population of cancer patients depends on three factors:

i) the proportion presenting with disease at a stage where it is treatable, and ideally curable

ii) the frequency of use and efficacy of treatment

iii) the prevalence of co-morbid diseases.

a) Stage at presentation (see also Chapter 8)

The clinical stage at which cancer is diagnosed is dependant on the biological behaviour of the tumour and the presenting symptoms. In order to make a diagnosis early it is critical that the patient is aware of the potential significance of any symptoms and that these are recognised as important by healthcare professionals. Some cancers, such as breast or skin, present with an obvious problem that is readily recognised and which instigates an urgent referral to a specialist. Other malignancies, such as ovarian and lung cancers, often present with a wide-range of non-specific symptoms, for example, fatigue, weight loss or shortness of breath, which can easily be attributed to other co-morbid diseases. This can result in a delay in diagnosis. However, for many cancers the propensity for early metastases means that by the time symptoms have developed, the disease has already spread to lymph nodes or other organs thereby reducing the chances of cure [152].

Cancer screening is potentially the most effective method to improve survival, by detecting cancers at an asymptomatic, often pre-invasive stage. Screening has proven particularly beneficial in cervical cancer where it is estimated that up to 91% of cervical cancer deaths, and around 18% of breast and colorectal cancer deaths, could be avoided [93]. For lung

cancer there is at present no effective method of screening, though large trials of CT scanning (with or without biological markers) are underway. In a large US trial, 484 tumours were detected in the 31,567 patients who underwent screening [90]. Of those lesions which were more than 36mm in size, 55% had already metastasised to lymph nodes or distant sites [91].

Screening with CT scans is heavily resource dependant in terms of both equipment and staff. In addition, the procedures required to confirm or refute the suspicion of cancer, are invasive, for example a thoroscopic biopsy. Consequently, the cost-benefit balance of CT screening is likely to be marginal

b) Treatment

Over the past half-century most cancer research has concentrated on understanding the biology of cancer, searching for new types of therapeutic agents and investigating these agents in clinical trials. But, however successful these agents are in clinical trials, all the money and effort are wasted, if these new therapeutic options are not available to the wider cancer population, and bring about an improvement in survival of the whole population.

Factors (other than stage at presentation) which have been shown to affect whether or not treatment is given, include patient's age, gender, race, performance status, co-morbid diseases, social deprivation, education, ability to pay for healthcare, and the proximity of cancer specialists. In some countries, organisation of health care is also a factor.

Although improvements in survival have occurred in the majority of other cancers, UK lung cancer survival rates have remained remarkably unchanged over the last 15 years [40]. Surgery and radical radiotherapy are effective treatments for lung cancer, but only a minority of patients are suitable for these treatments. Other therapeutic options, such as chemotherapy, have low efficacy in advanced disease and hence little impact on population-based survival. Consequently, if survival rates are to improve, the proportion of patients presenting with early stage disease receiving potentially curative treatment must be maximised, and more effective treatments need to be found.

c) Co-morbid diseases

Many of the older, population-based, series report only overall or crude survival. Although this is a useful measure, no account is taken of other causes of death, such as infectious diseases or ischaemic heart disease. This could have a significant impact on reported outcomes, particularly when comparing countries with very different disease profiles, such as developed and developing nations, or one with a much older population.

There are two principal methods of overcoming this problem:

1) Cause specific survival

Cause specific and progression free survival rates are frequently used in clinical trials when detailed medical record review can be performed to confirm the accuracy of the cause of death. However, in the population setting this is not practicable and the accuracy of death certification is variable. In lung cancer, where the disease has such a high mortality rate, it is often simpler for the medical practitioner to attribute death to the cancer, rather than seek

out other potential causes. Consequently, cause specific survival data will over-estimate the number of deaths due to lung cancer and therefore should be interpreted with caution.

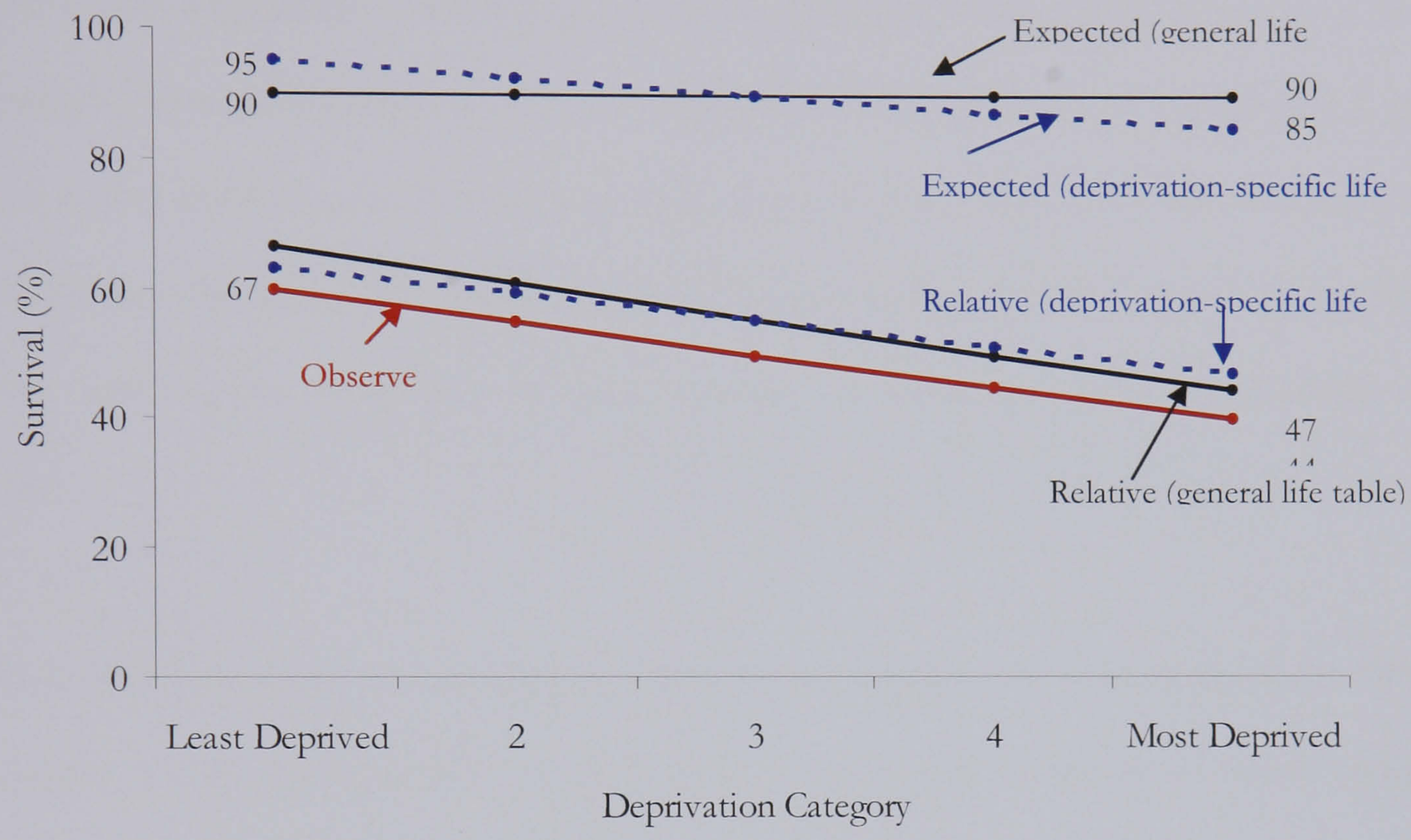
2) Relative survival

Relative survival compares the observed survival with the expected survival for a cohort of the general population with the same age and sex profile. It is therefore an estimation of the excess deaths due to cancer. When populations from two countries are compared and they have very different age profiles, then an age-adjusted relative survival, which weights the population to a standardised population, should be calculated.

However, it should be noted that the life-tables used to calculate the expected survival are for an average population and do not take account of different disease profiles within a population. This is a potential source of error when examining relative survival rates for lung cancer patients, as this group has a much higher rate of other diseases, than the general population.

Figure 2.1 demonstrates, using a hypothetical example, the impact of deprivation on life expectancy. Relative survival based on the general population will under-estimate the survival for the least deprived and over-estimate it for the most deprived. However, it has been estimated that using deprivation-adjusted life tables would only have an impact of less than 1% on the five-year survival rate of lung cancer in Scotland [186]

Figure 2.1 Difference in relative survival estimates when using deprivation-specific compared to general life tables (reproduced with kind permission from Diane Stockton [186])



d) Summary

When comparing survival outcomes from population-based series, it is important to note the following:

i) the distribution of clinical stages at initial presentation

ii) the rates of treatment use

iii) the methods of survival. reporting

International rates of treatment and survival for lung cancer

Over the last two decades, a vast amount of literature has been published reporting rates of treatment and lung cancer survival from various regions around the world. However, a direct comparison between countries is difficult, because of the wide variety of approaches to data collection and analysis used. Five-year survival rates vary from 16% in France and the USA, to 7% in the UK, Denmark and Poland [167]. These differences may represent genuinely inferior survival, but could also be demonstrative of differences in data collection and analysis.

EUROCARE is a collaboration of Cancer Registries in Europe and was set-up in the 1980's to evaluate cancer survival rates across Europe. The results of the most recent analysis pertaining to lung cancer are shown in Table 2.1 and demonstrate the wide range of survival figures reported, including neighbouring countries.

In an Editorial in Annals of Oncology, published to coincide with the release of the EUROCARE III data, Berrino [16] describes the potential difficulties of comparing population-based outcomes. The potential hazards are not only applicable to EUROCARE, but to the literature as a whole.

1) Population coverage:

There are wide differences in the proportion of the population covered by the different cancer registries. Table 2.1 includes the proportion of each nation's population covered by the European cancer registries. Only half of the EUROCARE countries collect data from all

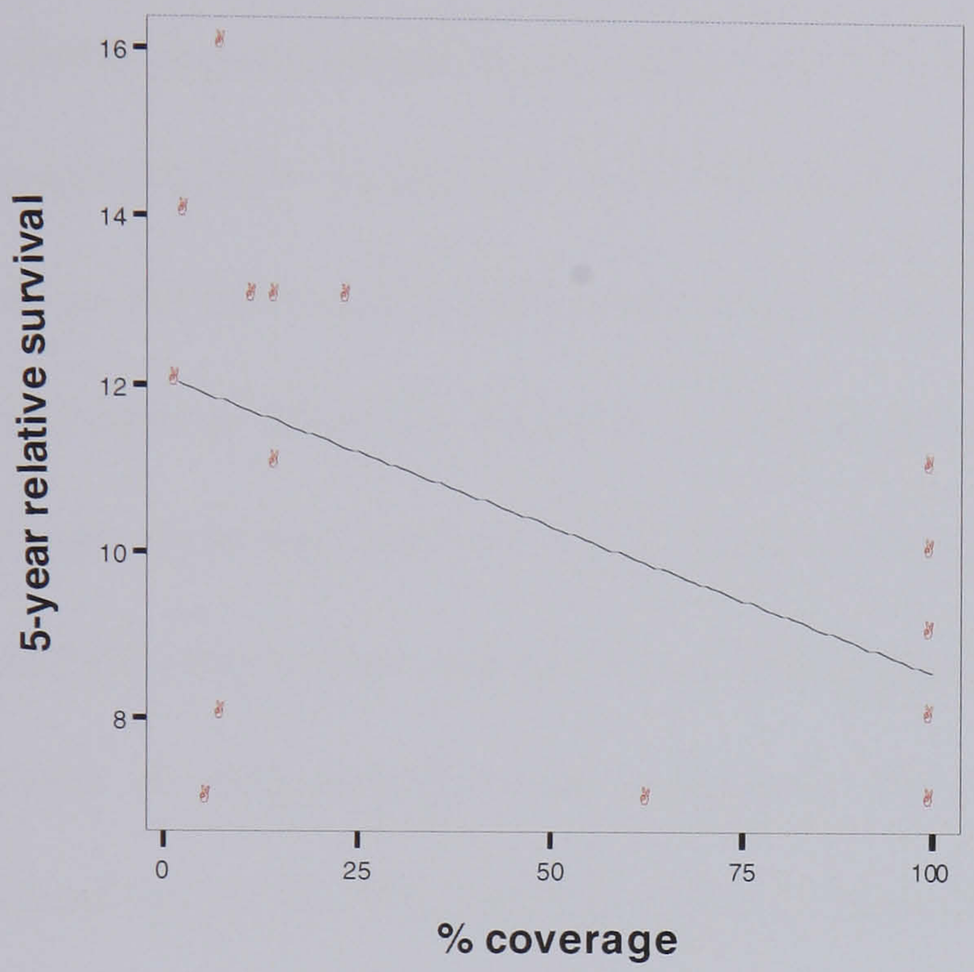
regions, the others only fund data collection in selected areas. In general, those registries with wider coverage report inferior survival. This is demonstrated in Figure 2.1 as a scatter diagram. In countries where the cancer registry is not centrally funded, there may be a bias towards collecting data in the more motivated regions, which are not necessarily representative of the treatment and outcomes of the wider population.

Table 2.1 Results of EUROCARE III (1991-1994) for lung cancer

	% of population covered	1-year relative survival[1]	3-year relative survival[1]	five-year relative survival[1]
Austria	8	41	19	16
Czech Republic	8	32	12	8
Denmark	100	25	9	7
England	63	22	9	7
Estonia	100	27	10	8
Finland	100	34	13	9
France	3	44	20	14
Germany	2	33	15	12
Iceland	100	33	15	11
Italy	15	36	14	11
Netherlands	24	38	16	13
Norway	100	30	12	9
Poland	6	28	10	7
Scotland	100	23	9	7
Slovakia	100	31	11	8
Slovenia	100	33	12	10
Spain	15	33	15	13
Sweden	100	32	13	10
Switzerland	12	38	18	13
Wales	100	18	9	8

[1] age-adjusted relative survival to account for different age distribution in each country

Figure 2.1 Box plot comparing cancer registry coverage and five-year relative survival



r=0.34

2) Catchment area:

Many studies which purport to be 'population-based', are in fact based on referral to a single institution or collection of hospitals[95, 191]. Although this might be reasonable in an illness with a high rate of pathological confirmation, it is not appropriate for lung cancer where up to a quarter of patients have a radiological diagnosis. Consequently, there may be gross under-reporting of community-diagnosed cases. These latter cases are not referred to hospital, either because of their poor performance status, or inability to pay for healthcare.

3) Case ascertainment:

The method of identifying cases varies greatly between cancer registries. In some countries, such as Denmark, all doctors are legally obliged to inform the cancer registry and therefore case ascertainment should be complete. At the other extreme, some registries do not record non-pathologically confirmed cases or 'death-certificate-only' cases, and therefore these registries will have much lower case ascertainment, particularly for lung cancer. As patients without a tissue diagnosis would be expected to have an inferior prognosis, primarily due to older age, excluding such cases will enhance the survival figures. In some countries, such as France, data protection regulations prohibit access to death certificate data [35, 132]. The omission of non-pathologically confirmed and death certificate only cases (which can represent up to 20-30% of lung cancer cases) could have a marked impact on survival figures.

4) Follow-up:

In-order to accurately quote survival figures, it is important to follow-up patients with records which are linked to cancer centres, hospitals and the registry of deaths. Many registries have active computerised links with the latter. This increased accuracy in identifying deaths and may make survival figures appear inferior if the follow-up of surviving patients is less assiduous[132]. Other registries do not have links to death registries outside their region and therefore they could potentially under-identify deaths [84]. This is a particular problem where there is a highly mobile population or cross-regional hospital referral.

5) Method of calculating survival:

As discussed earlier, in order to try and account for differences between populations, relative survival rates should be calculated. Relative survival takes into account the life expectancy, by age and gender for each specific population and therefore estimates the excess deaths due to cancer. If populations with very different age profiles are compared then age-adjusted relative survival should be calculated to standardise the population.

Though 'cause specific survival' can be used, it is well recognised (probably due to the lethality of the disease) that in lung cancer doctors readily attribute death to this disease and therefore other causes may be under-reported. Consequently, relative survival, rather than cause-specific survival, is a more appropriate measure for lung cancer.

Summary of published lung cancer series

A search of 'Pubmed' and 'Medline' was performed using the terms 'lung cancer and population' for all papers, written in English, published between 1995 and 2005. A total of 2796 potential papers were identified on 'Pubmed' and 2965 by 'Medline'. These lists were searched to identify those which reported data on population-based lung cancer treatment and survival. Next, reference lists in each publication were searched, to identify any previously unidentified papers.

Publications were excluded if they either

i) related to a hospital only registry

ii) analysed only a sub-group of patients, for example surgical cases only, or a minor pathological entity

iii) used patterns of care studies, where only the data on a sample of patients whose medical records were available, were selected.

A total of 45 publications were identified and the Tables below summarise the data (Table 2.2a = England and Wales, Table 2.2b = Rest of Europe, Table 2.2c North America, and Table 2.2d Australia).

When a research group published revised data on the same population, the most up-to-date information has been included in the tables. The publications underlined and in bold, represent those that most closely reflect the methodology used in this thesis.

England and Wales

Cancer care in England and Wales is almost entirely delivered by the National Heath Service (NHS), financed by taxes and free at the point of delivery. All patients should have equal access to healthcare.

Three cancer registry publications were identified, two examining treatment and survival of lung cancer patients and one general paper that reported data on the changes in lung cancer survival [37, 40, 99]. The papers from Yorkshire [37] and Thames [99] Cancer Registries both demonstrated low use of treatment, with between 44 and 86% of patients not receiving any. Reduced use of treatment appeared to be associated with increasing age, more advanced disease, deprivation (in Yorkshire), and area of residence. The rates of treatment, particularly surgery (7%) and radiotherapy (17%) were very low in South-East England. The survival rates reported were also low, with only 8% of patients alive at three years in South-East England, and 4% alive at five years in Yorkshire.

In a study reporting data from all England and Wales registries for the period 1996-99, Coleman *et al* [40] demonstrated the five-year relative survival rate of 6%, which was unchanged from the previous decade. Inferior survival rates were was observed in men who lived in deprived areas, but the impact of deprivation was less marked for women.

Rest of Europe

All member states of the European Union have some form of publicly funded healthcare with varying amounts of involvement of private facilities [132]. For example, in France employers pay 42% of gross salary and employees 21%, for healthcare that is delivered by public and private hospitals which both receive identical re-imbursement. In The Netherlands, healthcare is funded by obligatory deductions from wages into mutual insurance companies and the majority of cancer care is provided by state-run regional 'Comprehensive Cancer Centres'.

A number of studies have been published reporting data from France [68, 84, 114, 130]. The French Cancer Registries, due to data access restrictions, do not use death certificates for registration. The publications report data only on patients who have had a pathological confirmation. The series from Bas Rhin [68, 114] demonstrated an improvement in the median survival over the period 1981-1997 in SCLC patients, thought to be due to increased use of chemotherapy. There was also an increase in the number of patients having surgery, but there was no improvement in the survival of the patients with NSCLC. The reasons for the lack of benefit with the increase in surgery was uncertain, but the increased proportion undergoing resection for localised disease (110/180 (61%) 1982-5 to 162/202 (80%) 1994-7) would probably be insufficient to produce a statistically significant improvement in population-based survival.

Two groups from the Netherlands have published data [48, 101, 102]. De Rijke and colleagues from Maastricht and Limburg showed that of the patients diagnosed in 1997-8, 24% underwent surgery, 42% radiotherapy and 13% chemotherapy. 80% of patients with

localised disease were treated according to guidelines, but only 50% of patients with regional disease. The Eindhoven Cancer Registry have published a number of studies examining trends in treatment over time and the prevalence of co-morbidity in cancer patients [101-103]

In 2003, Mahmud *et al* published data [120] from the Republic of Ireland Cancer Registry. This series has high case ascertainment (96%). The use of treatment is similar to that seen in England and Wales; the surgical rate of 12%, radiotherapy 29%, chemotherapy 17%, with 50% receiving no treatment. The five-year survival rate was 9%.

North America

In the USA healthcare is privately funded, with Medicare providing insurance cover for those over the age of 65 years, and Medicaid for those on a very low income. Medicare is a Federal Insurance scheme with three levels of cover; Part A covering basic health care needs, Part B which includes screening, and the Prescription Drug Program, which covers drug costs. In addition to the insurance premiums paid whilst working, all patients have to pay other charges including 20% of doctor's costs, $1000 per in-patient hospital stay, and daily charges of $250-$500 per day for in-patient admissions exceeding 60 days.

Medicaid is run by each US State and has fixed poverty thresholds (around $1000 per month income for a family of four), below which healthcare costs will be covered. Up to a quarter of each State's budget is spent on Medicaid. However, many employees on low-income earn too much to be eligible for Medicaid, but are uninsured. In 2004, 68% of US citizens had

private insurance, 16% were covered by Medicaid and Medicare, and 16% (46 million US citizens) were uninsured (range 8% Minnesota to 25% in Texas) [1]. Only 60% of employers offer healthcare insurance and the average annual cost of private insurance for a family is $11,000.

A number of publications report data from the Survival Epidemiology and End Results (SEER) program of the National Cancer Institute. This collects data from 11 regions across the United States of America, representing around 14% of the US population. SEER captures around 97% of the incident cases in each region, collating data on tumour site, stage, and histology, date of diagnosis and cause and date of death. Patient related factors, such as age, gender, ethnic group, post-code (used to link with census data on income and education) are collected along with data on surgery and radiotherapy within four months of diagnosis. No chemotherapy data are collected. SEER only publishes data on patients with pathologically confirmed cancer.

The SEER publications [24, 57, 58, 73, 78, 153, 160, 162] and a number of other series [71, 127, 183] have examined the impact of factors such as race, social deprivation, and insurance-cover, on the treatment and survival of US lung cancer patients. These publications all report similar results with older patients, non-Whites and un-insured/Medicaid patients less likely to receive treatment. The impact of deprivation appears to be greater in the USA than in Canada where there is a publicly funded healthcare system [21, 77, 78].

The treatment rates in the USA are higher than that in UK. In Kentucky, for example, 30% receive no treatment, 24% undergo surgery, 37% radiotherapy and 29% chemotherapy [127].

In general, the survival rates are also higher in the USA than in Europe, with a five-year relative survival rate of between 16 and 11%, but the publications only report data on patients with pathological confirmation and often exclude 'death-certificate-only' cases. The impact of excluding these cases is difficult to quantify, but it is likely that the excluded cases have shorter survival.

Australia

Australian healthcare is provided by a mix of public and private hospitals funded by the State run healthcare system, supplemented by private insurance schemes. In principle all Australian citizens should have equal access to healthcare.

A number of comprehensive reports have been published examining the treatment and survival of patients with lung cancer in Australia [94, 163, 201, 202]. In general around a quarter of patients do not receive any treatment, a fifth surgery, and half radiotherapy. In one study, despite the universal access to healthcare, there was significantly less treatment delivered to patients in rural areas, though this did not impact on survival [202]. The survival rates appear similar to the UK, with an overall survival rate of 8% in New South Wales.

Conclusions

Much of the variation in the published lung cancer survival rates can be attributed to differences in the methods of collecting and reporting of the data. Whenever population-based survival rates are compared, it is important to appreciate the nature of the population from which the cases are collected, the methods of data capture and follow-up, and the exact survival measures quoted.

a) Stage at presentation

Though detailed data are not available in all series (and often for a sizeable minority the stage at presentation is unknown), generally around 30% of patients appear to present with localised disease. A further 30% have regional and 40% distant disease.

b) Treatment rates

The proportion of patients not receiving any treatment varies from around 30% in USA to 85% in parts of England. The rates of surgery ranged from 7% in Thames region to 24% in the Netherlands (32% in Detroit NSCLC), and use of radiotherapy from 17% in Thames to 56% in New South Wales. The use of chemotherapy also varied greatly; from 8% in Thames to 29% in Kentucky (series that include both SCLC and NSCLC).

Factors which affected the use of treatment appeared to be age, social deprivation (including insurance status, race and education), co-morbidity and sometimes simply health region of residence.

Method of reporting of survival

Reported five-year survival varies greatly from 6% in English Registries to 16% in Detroit, but the series differ greatly. The publications which give whole-population data including both pathologically confirmed and non-confirmed cases generally report five-year relative survival rates in the range 6-12%.

Table 2.2a Lung cancer treatment and survival in England and Wales

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Brown 1996[29]	Southend Lung Cancer Registry	1990-1992	563 (? 100%) (includes 16 DCO)	70% male, 73% histology PS 0-1 72%	49% no treatment within 2 months of diagnosis	-	Cases identified by hospital records and death certificates Patients seen by respiratory physician more likely to be treated (56% v 21%) Age strong determinant of treatment; for PS 0-1 patients treatment rate 86% <65 yrs v 39% 75+.
Cartman 2002[37][1]	Northern & Yorkshire Cancer Registry	1986-1994	22,654 (92%)	67% male 66% histology	51% (45-66) no treatment 11% (range 6-17) surgery 36% (23-43) radiotherapy 10% (5-13) chemotherapy	1yr OSR 21% 5yr OSR 4.4% 2yr resected OSR 50%	Ranges compare health authorities 1562 DCO & 364 for other reasons excluded 19% NSCLC surgery, 55% SCLC chemotherapy Region of residence appeared to be most significant factor affecting delivery of treatment; higher in those with greater proportion of patients managed by a specialist. Deprivation had minimal influence. The relative risk of death was reduced in regions with higher treatment rates.
Jack 2003[99][2]	Thames Cancer Registry	1995-1999	32,818 (81%)	64% male 75% histology 35% localised 30% distant	7% (range 5-12) surgery 17% (8-30) radiotherapy 8% (4-17) chemotherapy 72%(58-85) no treatment	1yr OSR 28% (11-34) 3yr OSR 11% (7-17%)	Ranges compare health authorities 7709 DCO excluded, if added 1 yr survival 22% Patients living in area with highest lung cancer rates had lowest use of treatment. Less likely to receive chemotherapy if from deprived area. More likely to be treated if first seen in a hospital with oncologists based there.
Coleman 2004[40]	All English and Welsh Cancer Registries	1996-1999	107,317 (79%)	63% male	-	5yr RSR 6.0% men and 6.5% women	No improved survival over the decade. Men from most deprived areas had significantly worse survival than those from affluent areas, but this difference was not observed in women

PS=Performance status, DCO = death certificate only diagnosis, OSR= overall survival rate, RSR= relative survival rate MS = median survival, RT=radiotherapy Chemo =chemotherapy, Mets= metastases, Charlson = score of co-morbidity[38]

[1]supersedes [129], [2] supersedes[150, 170]

Unlined = data similar to that presented in this thesis

Table 2.2b Lung cancer treatment and survival in rest of Europe

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Grosclaude 1995[84]	Calvados, Doubs and Tarn in France	1987-1988	615 (?)	90% male 98% histology	29% surgery (21-37%) 51% radiotherapy (40-70%) 30% chemo (20-39%)	18m OSR 30% Calvados and Tarn, 35% Doubs	No autopsy or DCO cases included Range of values between the different Departments Age main determinant of survival
Malmberg 1996[122]	West Sweden Cancer Registry	1976-1985	3285 (86%) Post-mortem and no pathology cases excluded	74% men Mean age 67 55% squamous 31% adeno 4% SCLC	19.5% surgery 6.6% chemotherapy	MS 5mo 5-yr OS 8% Surgical cases 5-yr OS 38%	23% cancer was an incidental finding Women had improved survival 10.1 v 7.6% 5yr Post-surgery tumour stage and age on predictors of outcome.
Janssen-Heijnen 1998[101]	Eindhoven Registry Netherlands **SCLC only**	1975-1994	1796(?)	13% women Mean age 65 1990-94 39% L-SCLC 36% E-SCLC 25% unknown	1990-1994 3.5% surgery, 4.3% RT only, 56% chemo only, 21.3% chemo + RT 27% none	1975-79 MS 5mo 1990-92 MS 9mo 2yr RSR 1975-79 7% 1990-92 8%	Women 7% cohort in 1975-79 and 19% 1990-4 Less use of intensive treatment in the over 70's 15% diagnosed autopsy or died<1 month Median survival improved but no improvement at 2-yrs.
Janssen-Heijnen 2004 [103]	Eindhoven Registry Netherlands **NSCLC only**	1995-1999	4076 (138 post mortem excluded)	19% women 27% localised 58% non-local 15% unknown 38% >age 70	19% surgery	Localised 3-yr RSR 47% 62% age <60 18% 80+ Non local 3-yr RSR 26% 31% <60, 13%80+	23% COPD, 23% ischemic heart disease
Engeland 1998[60]	Norway Cancer Registry	1954-1993	36,010 (~99%) excl DCO and autopsy	23% women Mean age 66 yrs 32% local 19% regional 42% distant 16% SCLC 17% no path	-	5-yr RSR ~5% men ~6%women Local 5yr RSR 16% men 19% women	Number without pathology declined from 26% in 1950s to 9% in 1990s Odds ratio death within 5yrs 0.8 1984-93 v 1954-63 for men and women Age and stage also affected odds of death as did path type with SCLC having inferior survival
Makitaro 1999 [121]	Northern Finland	1990-1992	602 (99%)	85% male 63% histology,	21% surgery (excluding autopsy cases)	-	25% lung cancer incidental finding 8 autopsy 75% bronchoscopy 60% CT scan No other treatment details given

Table 2.2b Lung cancer treatment and survival in rest of Europe

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Teppo 1999[194]	Finland	1955-1994	Not given >99% case ascertainment	-	-	5yr RSR 10% men 13% women	5yr RSR by stage Localised 29/38% men/women Regional 13/16% Metastatic 1 / 2%
De Rijke 2002[48]	East Netherlands, Maastricht and Limburg Registries **NSCLC + no pathology**	1997 - 1998	803 (?)	20% women 26% Stage I-II 34% Stage III 28% Stage IV 11% unknown 93% pathology 64% PS 0-1 19% PS2 12% PS 3-4 24%unknown	24.3% surgery 42.3% RT 12.8% chemo 26.7% no treatment Stage I-II: 67% surgery 15% Radical RT 11% no treatment	-	31% no serious co-morbid disease, 33% one, 19% two, 12% three or more. Stage I-II 5% FEV1 <1L, 52% 1-2.4L 82% Stage I-II treated according to guidelines - age over 75 or presence of ≥ 1 co-morbidity associated with reduced use 48% Stage IIIA and 54% Stage IIIB treated according to guidelines - age >75 main reason for not doing so.
Radzikowska 2002 [159]	Poland registered with a Research Institute	1995-1998	20561 (? covers 25% Polish population)	86% male, 81% histology, 18.8% women and 2.4% men non-smokers 57% PFS0-1	**Only available for those with histology** 25% surgery (15% all cases) 28.5% chemotherapy 14.5% radiotherapy 32% no treatment	**Only for patients with histology** MS 9.6mo men 11.2mo women	Only represents a proportion of population so biases compared with whole population unknown. Of those with histology 27% Stage I, 15% Stage II, 43% Stage III 15% Stage IV For patients with histology relative risk of death reduced if age<50, female, PFS0-1, adenocarcinoma, treated with surgery.
Lebitasy 2001[114] Mennecier 2003 [130]	Bas Rhin France **SCLC only**	1981-1994	787 (83%)	88% male, Median age 63 36% L-SCLC	84% chemotherapy (92% 1993-4) 30.5% thoracic RT	MS 12mo L-SCLC 7.2mo E-SCLC 2yr OSR 8.5% 5yr OSR 2.8%	17% excluded as no medical records 10.3% brain mets, 22% bone mets 35% cardiovascular disease, 25% COPD 1993-4 97% bronchoscopy, 92% thoracic CT, 87% CT brain, 30% bone marrow biopsy Survival improved over time L-SCLC (MS 9 to 14mo) and E-SCLC (MS 4 to 10mo)
Mahmud 2003 [120]	Republic of Ireland	1994-1998	7286 (96%)	66% male 76% histology	12.3% surgery 29.4% radiotherapy 16.5% chemotherapy 49.6% no treatment	5yr survival 9% (not stated if OSR or RSR)	65 autopsy and 3 other cases excluded 60% SCLC and 12% NSCLC chemotherapy 19.5% NSCLC surgery Healthboard and age, but not deprivation, were independent predictors of use of treatment

Table 2.2b Lung cancer treatment and survival in rest of Europe

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Talbäck 2003 [189]	Sweden	1994-1995	Not given >98% case ascertainment	-	-	1yr RSR 32% men 40% women 5yr RSR 10% men 17% women	No change over period 1970-1990
Foeglē 2005 [68]	Bas Rhin France **NSCLC only**	1982-1997	2028 (90% of a **random 40% sample** of all cases)	Data for 1994-7 (n=495) 13% women Median age 63 41% localised 20% regional 35% distant 4% unknown	1994-7 cohort 12% no treatment 33% surgery 32% RT 45% chemotherapy	1994-7 MS all 10.3mo localised 32mo regional 9.7mo distant 4.4m 5yr RSR all 15.7% 5yr RSR resected 41% 1yr RSR chemo only 24%	10% excluded had missing medical records 1994-7 cohort 54% squamous,30% adenocarcinoma, 10% large 96% thoracic CT, 96% bronchoscopy, 81% CT brain Increased use of surgery, chemo-radiation and chemotherapy alone over period 1982 to 1997 No improvement in survival over the period Survival influenced by age, stage, path type and treatment

Table 2.2c Lung cancer treatment and survival in North America

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Smith 1995[183]	Virginia age over 65	1985-1989	4999 (? 85%)	31% female 100% NSCLC 56% I-III 44% IV 63% Charlson 0	22.5% no treatment, 22.3% surgery 59% RT 2.2% chemo	2-yr overall Stage I-III resected 66% Stage IV 5%	Treatment within 6 months 36% Stage I-III surgery. Surgery less likely if older, low education, higher co-morbidity, urban residence Distance to RT made no difference
Greenwald 1998[82]	3 SEER regions **Stage 1**	1978-1982	5157		Surgery 59% (range 47-72% with income)	5-yr OSR 32%	In San Francisco black patients had lower odds of surgery even when lower income taken into account.
Bach 1999[10]	SEER **NSCLC Stage I & II only**	1985-1993	10,984 (14% coverage USA population)	38% female 100% NSCLC	Surgery 77% white patients 64% black patients	5-yr black, 39%, 43% white if had surgery, 4% v 5% if not	Charlson co-morbidity index similar black v. white patients. Inferior survival due to lower use of surgery.
Boyd 1999[21][3]	Ontario Cancer Registry v SEER	1987-1992	98% Ontario, 14% USA population	-	-	5-yrRSR Ontario 15.9% USA 14.2%	5-yr CSS 3.2% superior top quintile earnings compared to lowest in Ontario, 5.8% in USA. Poorest Canadians fared better than poorest Americans
Fry 1999[71][4]	National Cancer Database USA (covers 55% US hospitals)	1985-1995	713,043 **All pathological confirmation** 1995 78,307 case	1995 40% women 26% Stage I-II 33% Stage III 41% Stage IV 10% unknown	1995 19% no treatment 27% surgery 42% radiotherapy 30% chemotherapy	10yr RSR 7% 5yr RSR men 11% women 15% Stage I 42% Stage IV 1%	Only cases seen at participating hospitals so bias to patients referred to hospital 'no pathology' cases excluded Over period no change in proportion having surgery, but proportion not treated increased from 14 to 19%
Earle 2000[58] 2002[57]	SEER **Stage IV NSCLC only**	1991-1996	12,015>65yrs (14% coverage USA population)	40% women 72% Charlson 0 19% 1 9% 2+	26% chemotherapy (25% 1991, 30% 1996)		Over 65 so could link to Medicare billing database (1991-1993 11.5% COPD, 4.5% heart failure,4% cerebrovascular disease, 1.6% previous MI) Age, race, region, income, Charlson and type of hospital all affected use of chemotherapy – appears to be linked with increased odds of referral to Oncologist – if saw Oncologist then only age and co-morbidity main determinants of treatment
Gorey 2000 [78][5]	Toronto + 3 US cities	1986-1988	2075 (97%)	-	-	5-yr RSR Ontario women 18-15% Detroit women 16-10%	Socially deprived Canadians had improved survival compared to deprived Americans Canada's universal healthcare and different health care organisation may negate some of the negative impact of poverty.

[3] supersedes[118], [4]supersedes[70] [5] supersedes[77]

Table 2.2c Lung cancer treatment and survival in North America

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Bradley 2001[24]	Michigan	1996-1997	12,096 (95%+)	42% women 18% local, 25% regional	-	-	Later presentation and increased lung cancer mortality in younger patients on Medicaid
Gadgeel 2001[74] / Ranalingam 1998[160]	Detroit SEER **100% pathology**	1973-1998	48318 (? 100%) (second paper 1973-1992 looking at +/- age50	35% women 23% black Median age 65 22% local 24% regional 45% distant 9% unknown	1973-1992 16% no treatment 32% surgery 34% chemotherapy 51% RT	5-yr RSR 1973-1985 white 13% v 11% black (ns) 1986-1998 white 16% v 11% (p<0.001)	Greater improvement in survival in white patients over recent years than in black patients On multivariate increased risk death in black patient, men, older patients, 'not-adenocarcinoma', first era of data collection. In second study younger patients more likely to receive treatment. Also improved survival only in loco-regional disease over period 1973-1993.
Barbera 2003[12]	Ontario and SEER in USA	1994-1996	30,688 (98%)	37% women Median 68yr 80.3% pathology	In Ontario 32.5% RT within 1yr (range 22.8-43.3% by counties) In SEER regions 44.2% RT within 1yr	-	Benchmarking study to look at RT use in Canada and USA No variation in use of RT with travel (+/-30km) or socio-economic status. Lower use in counties with longer waiting times
McDavid 2003[127]	Kentucky	1995-1998	12,477 (? 100%)	38% women 21% local 26% regional 41% distant	30% no treatment, 22% surgery 37% RT 29% chemo	3-yr RSR 19% women 14% men	Survival improved in privately insured v. uninsured
Demeter 2003[50]	Alberta	1998	611 (83%)	45% women Mean age 66.5 17% SCLC 21% Stage I-II 33% Stage III 7% Stage IV	NSCLC 27% Surgery 74% RT SCLC 72% chemotherapy 70% RT	2-yr OS 24% NSCLC, 10% SCLC	Stage chemotherapy and surgery associated with improved survival for NSCLC, stage and chemo for SCLC
Laskin * 2004[113]	British Columbia Canada **SCLC only**	1990 and 1995	628	45% women Median age 67.5 34% L-SCLC 66% E-SCLC	L-SCLC 82% chemo E-SCLC 70% chemo	MS L-SCLC 12mo E-SCLC 5.6mo	Use of early thoracic RT in l-SCLC increased from 17% in 1990 to 63% in 1995. Early RT 5-yr OS 16% v 9.6% if started >6weeks after start chemo
Ramsay 2004[162]	SEER **NSCLC Stage III & IV only**	1994 & 1999	4851 (14% coverage USA population)	43% female Median age 75yr 49.2% III 50.2% IV	1994 38% no treatment, 9% surgery, 47% RT 25% chemo 1999: 31% no treatment, 7% surgery, 48% RT 43% chemo	MS chemo 8mo without 5mo	Less likely to receive chemo if male, non-white, Stage IV, Charlson >1, lived in Hawaii.

* Includes some of the same patients as this thesis

Table 2.2c Lung cancer treatment and survival in North America

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Potosky 2004[153]	SEER **NSCLC only**	1996	898 **random sample** (14% coverage USA population)#	44% female 100% NSCLC 27% Stage I&II 33% III 40% IV	Stage I & II 5% no treatment 79% surgery 16% radiotherapy Stage III 21% no treatment, Stage IV 28% no treatment 31% RT 41% chemo	-	52% patients received recommended therapy. Less likely if non-white, age over 75, not married.
Campling 2005[33]	Pennsylvania	1995-1999	28,789 (? 100%)	100% men 64% NSCLC 14% SCLC 22% 'other' (?no pathology) 22% **local** 26% regional 43% distant	-	MS 7.8mo local 22mo regional 12mo distant 4mo 5-yr 15%	Patients receiving healthcare in Veterans Administration Hospital had inferior survival possibly due to increased poverty and co-morbidity
Fu 2005[72]	SEER **100% pathology**	1975-1999	228,572 (14% coverage USA population)	36% women 18% local 28% regional 44% distant 10% unknown	Surgery 26.8% men, 28.5% women RT 51.3% men, 47.3% women	1988-99 5yr RSR 13.8%men 17.3%men	Excluded 13.7% previous cancer, 2.1% DCO, 6.8% no pathology, 9.5% not squamous, adeno, large or small cell types 45% adenocarcinoma in women v 33% men Local disease 64% women and56% men had surgery Women with surgery 5yr RSR 57% v 48% men
Ugnat 2005[198]	Canada except Ontario & Quebec	1989-1991	-	-	-	5-yr RSR 11% men (9-15%) 15% women (11-21%)	Examines the variation in survival between the Canadian provinces
Wisnivsky 2005[208]	SEER **NSCLC Stage I only**	1991-2000	16,036 (14% coverage USA population)	47% women	Surgery 86%	5yr OSR 54% Hispanic 62% Whites	Surgery less likely in Hispanics Operated cases had same survival No difference in non-cancer related deaths suggesting inferior outcome due to not being offered surgery not co-morbidity

Patterns of care study but included as includes some useful data

Table 2.2c Lung cancer treatment and survival in Australia

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Vinod 2003[201] & 2004[202] Hui 2004[94]	New South Wales Australia	1993-1996	527 (?100)	30% women Median age 68 55% PS 0-1 45% PS 2-4 75% NSCLC 15% SCLC 10% no path	28% no treatment 19% surgery 56% RT 21% chemo NSCLC 25% no treatment, 24% surgery, 60% RT, 11% chemo SCLC 13% no treatment, 6% surgery, 55% RT, 83% chemo No path 80% no treatment 20% RT	MS 6.7mo 1yr OSR 33%, 2yr OSR 16%, 5yr OSR 8% MS L-SCLC 17mo E-SCLC 5mo Stage I 32mo Stage II 19mo Stage IIIA 11mo Stage IIIB 7mo Stage IV4.4mo	91% thoracic CT scan, 56% bronchoscopy, 36% bone scan, 20% brain CT scan, 25 PET scan Vinod 2004 paper examines the three different regions in NSW in 1996. Patients in the more rural area were less likely to have pathological confirmation and treatment with radiotherapy or chemotherapy. Survival did not vary between the regions. Hui 2004 looked at the two non-rural areas in 1996 – and demonstrated no impact with respect to diagnosis, treatment nor survival with socio-economic status
Richardson 2000[163]	Victoria Australia	1993	868 (82% returned questionnaires)	30% women Median age 69 83% PS 0-1 73% NSCLC 14% SCLC 12% no path SCLC: 25% limit 52% Extensive NSCLC: 23% local 9% regional 37% distant 30% unknown	28% treated with curative intent 25% no treatment 23% surgery 44% RT 18% chemo	5yr OSR 11%	68% thoracic CT scan. 19% COPD, 11% ischaemic heart disease 71% SCLC chemotherapy

Table 2.2c Lung cancer treatment and survival in rest of the world

Author	Population	Period	Number (% of registered)	Characteristics	Treatments	Survival	Comments
Graupera Boschmonar 1999[81]	Cuban Cancer Registry	1988-89	2775 (40%) DCO (52%) and lost (8%) excluded			3yr RSR 11% - after DCO and lost excluded	Only represents a minority of cases so true population survival data unknown
Yeole 2005 [212]	Mumbai Cancer Registry	1992-94	1230 DCO (14%) excluded	20% women 29% no pathology 39% local 30% mets	_	5-yr RSR 16%	Reduced hazard of death with younger age, stage and Muslim religion

Chapter 3

Lung Cancer in British Columbia in 1995: treatment and survival

Methods

The British Columbia Cancer Registry was set up in 1969 and is closely linked with the Province's four cancer centres which make up the British Columbia Cancer Agency (BCCA). This association has enabled integrated data collection with computer linkage of cancer registration and treatment details. The case ascertainment of the cancer registry in 1995 was estimated as 93.5%. This is not as high as in some countries such as Scotland, primarily due to a more mobile population. Cases are identified primarily through pathology reports and death certificates.

Ethical approval from the University of British Columbia Clinical Research Ethics Board was obtained for this study.

1) Data Collection

i) Data available from cancer registry

The following data are collected:

Name

Gender

Date of birth

Address including postcode

Date of diagnosis – defined as date of pathological confirmation, or if not performed the date of radiological or clinical diagnosis

Method of diagnosis (pathology, cytology, autopsy, radiological, clinical)

Pathological type

Site of tumour

Stage of tumour – TNM where available, if not, global staging (I-IV)

Date of death

Cause of death on death certificate

ii) Data from British Columbia Cancer Agency Database

Referral – if seen in BCCA

Radiotherapy

Date of first fraction

Site of treatment

Intention of treatment as specified by treating physician

Dose delivered

Fractions

Chemotherapy – all chemotherapy directly supervised by a BCCA Oncologist.

Chemotherapy agents delivered

Date of first cycle

Date of last cycle

Follow up

Date last seen

iii) Data from BCCA pharmacy database

In British Columbia, community oncologists, internal medicine specialists who have spent time training in oncology, deliver some chemotherapy. In remote communities general practitioners, under the supervision of an oncologist, also give some oral chemotherapy. However, all chemotherapy is dispensed by a BCCA pharmacy; therefore it was possible to identify all patients receiving chemotherapy in the community using the pharmacy database.

Chemotherapy

Type of agents used

Date of first cycle

Date of last cycle

iv) Data from Medical Services Plan

Surgery is an important treatment modality used in lung cancer. In British Columbia (BC) the surgeons who perform lung cancer resections work in a variety of teaching and community hospitals that do no have direct links to the BCCA. Therefore, in order to identify the patients that underwent a resection an alternative approach was required.

Though the members of the staff of the BCCA are salaried, other doctors in BC work on a 'fee-for-service' basis, billing the Medical Services Plan. This is a comprehensive insurance scheme run by the Provincial Government. Therefore, details on all hospital admissions, investigations, and operations are available from this source.

A list of the patients diagnosed with lung cancer in 1995 identified by the Cancer Registry was supplied to the MSP who then conducted a match with their database, and provided details on the following.

Diagnostic procedures – CT scans, bronchoscopy, CT guided biopsy, and the speciality of the doctor who conducted this

Staging procedures e.g. mediastinoscopy

Surgery – nature of operation performed e.g. pneumonectomy, lobectomy etc.

v) Data from General Practitioners (see Appendix 1 for questionnaire)

Some patients had not been referred to BCCA, nor had received any cancer therapy therefore, in an attempt to try and obtain further information on these patients; letters were sent to the patients' general practitioners.

Unfortunately, though letters were sent to more than 500 GPs, only 290 replies were received, of which only 127 (25%) could provide useful information. In BC, the GPs are only required to keep their records for five years after death; so many sets of files had been destroyed.

The following information was requested:

Method of diagnosis

Stage of disease (localised, regional or metastatic)

Any treatments received and where

If the patient was not referred for treatment, why not (refused, dying, felt not to be appropriate etc)

2) Collation of information

From the Cancer Registry, all patients diagnosed with lung cancer (ICD-9 162; ICD-10 C33-C34) in British Columbia between 01 January 1995 and 31 December 1995 were identified and an SPSS database created. Using the patient's unique Canada Care identification number and file merge techniques, the data from the MSP, pharmacy and the GPs were added to the database.

Then, in order to enable comparison with the previously collected Scottish data the time from diagnosis to each procedure or treatment was calculated, and any treatments that commenced more than six months after diagnosis were excluded. An exception was made for consolidation radiotherapy for limited stage small cell lung cancer (SCLC), when the radiotherapy is part of the 'initial treatment package', but can start seven months after commencing chemotherapy.

Then new variables were derived

1) **Age at diagnosis** - this was grouped into four categories aged under 60, 60-69, 70-79 and over 80 years.

2) **Distance to cancer centre** – in previous studies in BC a travelling distance of more than two hours to a cancer centre was defined as 'long' [92]. Travel times have previously been calculated for each post-code.

3) **Income** – The average household income for each post-code can be derived from census data. In 1998, the median household income in BC was $CDN48, 800. This is the only data on the distribution of household income in the population that could be obtained from the Canadian Census website. There was little change in income over the period 1995 to 1998 so this value was used to divide the population into two groups. The income was also divided into five groups <CDN$40,000 per annum, 40-49K, 50-59K, 60-69K and 70+K.

4) **Summary pathology** - the following groups were formed: small cell, squamous cell, large cell, adenocarcinoma (including bronchoalveolar), non-small cell lung cancer not otherwise specified (NSCLC-NOS) and other (included types such as acinar, or spindle cell).

5) **Clinical summary stage** – in order to match the Scottish data the stage was also classified as either 'local', 'regional' or 'metastatic', corresponding to node negative, involved lymph nodes, and presence of metastasis, respectively. This does not correspond exactly with the more conventional Stage I-IV staging system as T1-T4N0 = localised and TxN1-3= regional, but is easier to apply when data for staging investigations is limited. Cases with limited stage SCLC were defined as 'regional' and extensive 'metastatic'. Some unstaged patients had a date of diagnosis the same as the date of death. There was obviously no time to perform staging investigations so these patients were defined as 'autopsy' stage.

6) **Potentially curative therapy** – this was defined for NSCLC as either a resection (segmentectomy (including wedge resection), lobectomy or pneumonectomy) or radical radiotherapy with a dose of at least 50Gy. A number of patients received radiotherapy with an intent described as 'radical' by the treating physician, but to a dose of less than 50Gy. A

similar discrepancy occurred in the original analysis of the Scottish data [62]. Therefore, in order to ensure a uniform approach with the various fractionation schedules, and as it is exceedingly unlikely that a dose of less than 50Gy would be curative; this approach was also adopted for the BC patients.

For those patients with limited stage SCLC potentially curative treatment was defined as chemotherapy combined with either thoracic radiotherapy with a dose of at least 30Gy (chemoradiation), or with surgery.

7) **Palliative treatment** was defined as any treatment delivered out-with the definitions defined above.

8) **Chemotherapy** – the regimens were combined to form two groups; multiple agents or single agent /unknown regimen.

9) **Survival time** – calculated as the time from date of diagnosis to date of death or date last seen. Patients who died the same day as an operation had their date of diagnosis moved one day forward to ensure their inclusion in the analysis of treatment delivered.

10) **Cause of death** – the primary and secondary causes of death were available. Those patients with lung cancer as primary cause of death, or with lung cancer as secondary cause of death, but an obvious linkage with lung cancer, for example pneumonia, were defined as having had died of lung cancer. Other causes of death were combined to form a single group of patients with 'other cause of death'. However, in lung cancer it is well recognised that

many patients are certified as dying of lung cancer when this may not represent the genuine cause of death, so any cause-specific survival analysis should be interpreted with caution.

3) Statistical Analysis

The majority of the data were analysed using descriptive statistics. Associations between variables were assessed using chi-squared for grouped data and Analysis of Variance (ANOVA) for continuous data. To examine the factors that affected treatment delivery chi-squared analyses and multivariate logistic regression analyses were conducted. The latter was performed using dichotomous and categorical variables to calculate the odds of receiving treatment. Kaplan Meier survival analyses were conducted to plot survival curves and to estimate the median, one, two and five-year survival. Factors affecting survival were examined using log rank tests and Cox's proportional hazard regression analyses.

All p values of less than 0.05 were deemed statistically significant, though those greater than 0.01 should be interpreted with caution due the large number of statistical tests performed.

Results

1) Demographics and tumour factors

2256 patients were identified, with a median age of 70 (range 22-100). There were 1323 men (58.6%) and 933 women. 647 (28.7%) patients lived more than a two-hour drive from a Cancer Centre. The median income was lower than the BC average at $CDN 46,670 (mean 48,206 sd 9615) and 56.3% of the population lived in an area with below the median household income for British Columbia.

The diagnosis was confirmed with histology in 55.5%, cytology 25.2% (ante-mortem pathological confirmation rate of 80.7%). A radiological/clinical diagnosis was made in 11.5%, at autopsy in 1.4%, and the method of diagnosis was unknown in 6.3%. In 1032 (45.7%) cases, the tumour was located in the upper lobes, 454 (20.1%) the lower lobes, 144 (6.4%) main bronchi, 102 (4.5%) right middle lobe, 26 (1.2%) were multi-focal and in 498 (31.1%) the site was unknown.

Of the 1850 (82%) patients with pathological confirmation, 636 (34.3%) had adenocarcinoma, 477 (26.7%) squamous cell, 307 (16.6%) small-cell, 222 (12.0%) large cell, 177 (9.5%) NSCLC not otherwise specified (NSCLC-NOS), and 31 (1.7%) other pathological types. No pathological confirmation was obtained in 406 patients.

For the purposes of analysis, three large pathological groups were defined; no pathology, small cell and NSCLC, the latter consisting of all the remaining pathological subtypes. Historically this division was made as SCLC was managed primarily with chemotherapy and

NSCLC with surgery and radiotherapy, though this distinction applies less so now than in the past. There were no significant differences in the distribution of gender, distance to cancer centre between these three groups (χ^2 $p>0.05$) or income (ANOVA $p>0.05$), but the 'no pathology' group was significantly older (ANOVA mean age 'No path' =76, SCLC =67, NSCLC =67 years $p<0.001$)

Detailed information on staging was available for 1472 (65.2%) patients (Table 3.1a) and less detailed staging using the local: regional: metastatic system (LRM) for 1975 (87.5%) cases (Table 3.1b). This additional information came either from the GP questionnaires or was derived from treatment; for example, if the patient received radiotherapy for bone metastases soon after diagnosis they were deemed to have had stage IV disease at presentation.

Table 3.1a Distribution of stage at presentation

	IA	IB	IIA	IIB	IIIA	IIIB	IV	LIMIT	EXTENT	UNKNOWN
NUMBER	155	188	20	119	173	176	383	104	154	784
%	6.9	8.3	0.9	5.3	7.7	7.8	17.0	4.6	6.8	34.8

Table 3.1bDistribution of stage using broader groups

	LOCALISED	REGIONAL	METASTATIC	AUTOPSY	UNKNOWN
NUMBER	498	538	756	183	281
%	22.1	23.8	33.5	8.1	12.5

2) Staging and treatment

For the following analyses, the 183 patients who died on the same day that their diagnosis was made were excluded as there would have been insufficient time to either conduct investigations or administer treatment. This excluded group contained 59% men, median age was 78 years (mean 76.6 sd 10.4), 29% lived more than two hours from a cancer centre, the median income was $CDN 48,230 (mean 46,900 sd. 10500) and only 33 (18%) had had pathological confirmation (23 at autopsy). This group was significantly older ($p<0.001$), and obviously was less likely to have had pathological confirmation ($p<0.001$) than the main group.

i) Staging Investigations

Of the remaining 2073 patients, 1526 (73.6%) underwent a CT scan and 1288 (62.2%) had a bronchoscopy. 494 (23.8%) of patients also had a mediastinoscopy.

ii) Any treatment

546 (26.3%) patients were treated with potentially curative intent, 826 (39.8%) palliative treatment and 701 (33.8%) did not receive any treatment in the first six months following diagnosis.

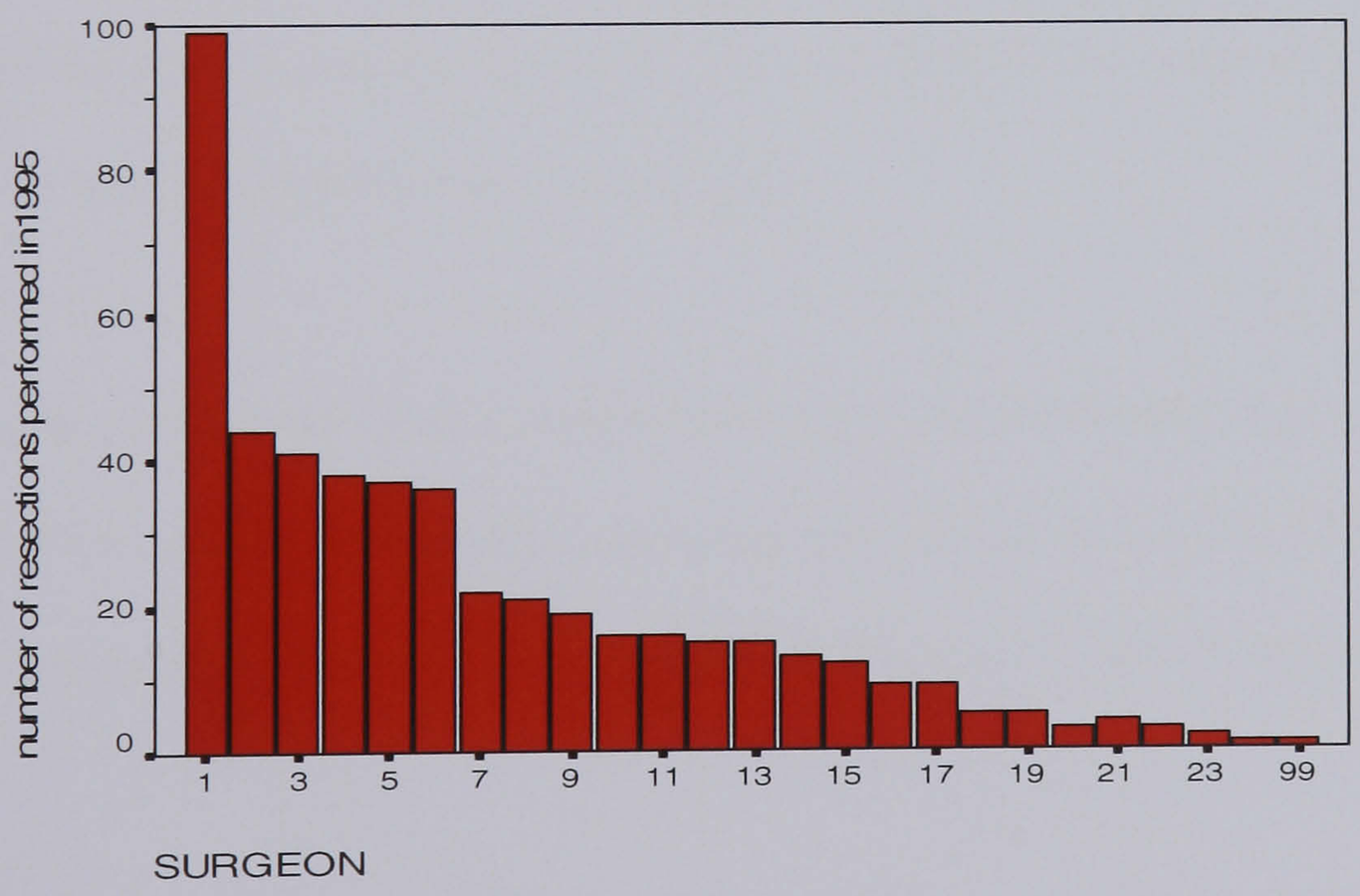
iii) Surgery

489 patients (23.6%) underwent an attempted resection, for 51 (10.2%) patients (2.5% of the population) this was an 'open-shut' thorocotomy, and 438 had a cancer resection.

The median age of the surgical patient was 67years (mean 65.5, range 32 to 84), which was significantly younger (ANOVA $p<0.001$) and the median income at $CDN47, 700 was higher than those not undergoing surgery (ANOVA $p=0.03$).

Lobectomy was the most frequently performed operation with 317 (15.3% of population) patients undergoing this type of resection, 83 (4.0%) had a pneumonectomy and 38 (1.8%) segmentectomy. Twenty-five different surgeons performed the operations (figure 3.1) with a median number of five operations per year (range of 99 to 1). Six surgeons performed 62% of the resections. Twelve patients died within 30 days of resection and three post-thoracotomy; giving a 4.8% post-operative mortality rate for pneumonectomy, 1.9% for lobectomy and 6% post-thoracotomy (3.1% for all operations). This rate is in keeping with other published series from this era [51].

Figure 3.1 Number of operations performed by each surgeon



The final pathological stage of the 438 resected tumours is shown in the Table 3.2.

Table 3.2 Distribution of pathological stage

	1A	1B	IIA	IIB	IIIA	IIIB	IV	LIMIT	Unknown
Number	119	118	17	68	41	16	10	8	41
% of resections	27.2	26.9	3.9	15.5	9.4	3.7	2.3	1.8	9.4

The most common pathological type was adenocarcinoma, which occurred in 205 (46.8%) patients, 136 (31.1%) had squamous cell, 40 (9.1%) large cell, 8 (1.8%) SCLC, 16 (3.7%) NSCLC-NOS, 28 (6.4%) other and in five cases the type was not recorded.

Thirty-four patients with NSCLC received high dose pre or post-operative radiotherapy (PORT) (one patient underwent radical radiotherapy delivered to a second lung cancer), and three of the SCLC patients received adjuvant treatment. Most of the NSCLC patients who received PORT had either Stage IIA (38.2%) or Stage IIIA (29.4%). Unfortunately the indication for PORT, for example positive resection margin, was not recorded. The time from surgery to post-operative radiotherapy ranged from 22 to 132 days. Within the first six months palliative radiotherapy to the chest was delivered to eight of the surgical patients, and eleven received radiotherapy to other sites.

Twenty patients who had a resection received chemotherapy, only one pre-operatively. The time from operation to starting chemotherapy ranged from 16 to 173 days (median 53 days). The most commonly used regime was vinorelbine and cisplatin (8 patients, 40%).

iv) Radiotherapy

836 (40.3%) of patients received radiotherapy in the first six months following diagnosis. The first course of treatment was radical radiotherapy to a dose of ≥50Gy for 45 patients (2.2% population), 34 (1.6%) pre or post-operative radiotherapy, 67 (2.9%) adjuvant thoracic treatment for SCLC, 533 (26%) palliative radiotherapy to the chest, and 158 (7.6%) palliative radiotherapy elsewhere.

A second course of radiotherapy was delivered at some point during their lifetime to 275 patients (40 patients prophylactic cranial radiotherapy (PCI) and 235 palliative treatment), 44 patients received three courses of radiotherapy, 14 four courses, 5 five courses, 1 seven and 1 eight courses of treatment.

Of those patients who did not receive radiotherapy during the first six months, 21 went on to do so later. Therefore the population lifetime use of radiotherapy was 41.3% (38% including 'autopsy' cases).

Ten patients had the radiotherapy intent defined by their oncologist as 'radical', but received a dose of <50Gy (range 10-48Gy mean 35.3Gy). For the remaining 45 patients, the dose ranged from 50 to 60Gy (mean 52.4Gy) with a median fractions of 20 (median 20.6, range 15-30). The most commonly used fractionation schedule was 50Gy in 20 fractions (16 patients).

For the 34 patients who received post-operative radiotherapy the median dose was 50Gy (range 20-65Gy mean 49.7Gy) with median of 20 fractions (mean 19.7).

Chemoradiation was delivered to 67 patients (57%) with limited-stage SCLC. The median dose used was 40Gy (range 30-55.2Gy). A dose of 40Gy in 15 fractions was used for 67.2% of patients.

For those patients who received palliative radiotherapy to the chest the commonest fractionation schedule was 20Gy in five fractions (range 5-48Gy). 43.6% of patients received a dose of 20Gy in 5 fractions, 22% 30Gy in 10 fractions and only 4.8% of patients had a single fraction treatment using between 8 and 10Gy. Sixteen patients received brachytherapy as their initial palliative radiotherapy treatment.

Similarly, the most frequently used fractionation schedule for 166 treatments delivered to other sites (56.3% bone, 40.5% brain) was 20Gy in 5 fractions (50.9% of treatments). The doses ranged from 6 to 44Gy in 1 to 16 fractions.

During the first six months following diagnosis a total of 8409 fractions of radiotherapy were delivered, 6778 (80.6%) as part of the first treatment course and 1360 in the second. 2821 fractions (33.5% of total) were used as part of curative therapy, either during radical, adjuvant or post-operative radiotherapy.

v) Chemotherapy

A total of 368 (17.3%) of the 2073 patients received chemotherapy, 285 of whom received a platinum based regime. The three most commonly used regimes were PAVE (cisplatin, adriamycin, vincristine and etoposide) 85 cases, PNAV (cisplatin, vinorelbine) 75 cases, and alternating EP/CAV (etoposide, cisplatin / cyclophosphomide, adriamycin, vincristine) 62 cases.

The median time between diagnosis and commencing chemotherapy was 19 days (mean 28.6 0 to 175 days). The number of cycles was not recorded, but the date of the first and last cycle was available and could be used as a surrogate. The median time between these two dates was 58 days (mean 62 days). The majority of chemotherapy protocols used had a 21-day cycle length so this approximates to an average of 4 cycles per patient. 23% of patients received only one cycle of chemotherapy (<21days) and 14% two cycles (21-42 days). 37 (10%) patients died within a month of starting chemotherapy.

3) Treatment combinations by pathological groups

i) Small Cell Lung Cancer

There were 306 patients with SCLC, 36% of whom had limited stage disease. The treatment combinations are shown in Table 3.3.

Table 3.3 Treatment delivered patients with SCLC

	Number	%
Surgery* only	3	1.0
Surgery and chemotherapy	2	0.7
Surgery, chemotherapy and post operative radiotherapy	3	1.0
Chemotherapy and adjuvant thoracic radiotherapy	64	20.9
Chemotherapy	91	29.7
Chemotherapy and palliative radiotherapy	71	23.2
Palliative radiotherapy	22	7.2
None	50	16.3

* = Resection

76 patients received PAVE, 62 patients received EP/CAV, 40 oral etoposide, 26 CAV, 19 EP, 8 other various regimes.

Of the 111 patients with limited stage disease, 72 (64.9%) received potentially curative treatment (chemoradiation or surgery +/- chemotherapy), 34 (30.6%) palliative treatment and 5 (4.5%) no treatment. There were 168 individuals with extensive stage disease of whom 134 received palliative treatment (81%). Of the 27 unstaged patients, 14 received chemotherapy and 13 no treatment.

Therefore, 75.5% of the SCLC patients received chemotherapy as a component of their initial treatment. Of these 25 (10.8%) died within a month of commencing chemotherapy, 4 of 94 (4.2%) with limited stage disease, 17 of 123 (13.8%) with extensive disease and 4 of 14 (28.6%) the unstaged patients.

ii) Non-Small Cell Lung Cancer

A total of 1540 patients were diagnosed with pathologically confirmed NSCLC. The distribution of management is shown in Table 3.4.

Table 3.4 Treatment delivered patients with NSCLC

	Number	%
Surgery only	364	23.6
Surgery and chemotherapy	8	0.5
Surgery, chemotherapy and post operative radiotherapy	5	1.9
Surgery, chemotherapy and palliative radiotherapy	1	0.1
Surgery and post operative radiotherapy	29	1.9
Surgery and radical radiotherapy	1	0.1
Surgery and palliative radiotherapy	17	1.1
Radical radiotherapy	38	2.5
Radical radiotherapy and chemotherapy	3	0.2
Palliative radiotherapy	499	32.4
Chemotherapy	60	3.9
Chemotherapy and palliative radiotherapy	56	3.6
None	459	29.8

Potentially curative treatment (surgery or radical radiotherapy) was used in 30.3% of patients; palliative treatment in 39.9%, and 29.8% received no treatment. The management intent, broken down by the extent of disease, is shown in Table 3.5 and demonstrates that two-thirds of patients with localised disease were treated with curative intent, and one-third of patients with regional disease.

Table 3.5Treatment intent and stage at presentation

χ^2 with $p<0.001$	Localised	Regional	Metastatic	Unknown	Total
potentially curative	292	128	12	34	466
	65.6%	31.7%	2.3%	19.2%	30.3%
palliative	92	192	322	9	615
	20.7%	47.5%	62.6%	5.1%	39.9%
none	61	84	180	134	459
	13.7%	20.8%	35.0%	75.7%	29.8%
Total	445	404	514	188	1540

113 patients died within a month of commencing treatment, 12 (2.6%) receiving potentially curative and 101 (16.4%) with palliative treatment.

Of the 133 NSCLC patients who received chemotherapy, the most commonly prescribed regime was cisplatin and vinorelbine, which was delivered to 74(56%) patients. Of the 133 patients with NSCLC nine (6.7%) died within a month of starting chemotherapy.

iii) Patients without pathological confirmation

A total of 227 patients did not have a pathological diagnosis recorded on the BC Cancer Registry database. Five of these patients underwent a resection so pathological type would have been available, but had not been recorded. Localised disease was present in 53 patients, 23 had regional and 74 metastatic disease. The stage was unknown in 77 individuals. The management used for this group of patients is shown in Table 3.6.

Table 3.6 Treatment delivered patients without pathological confirmation

	Number	%
Surgery only	4	1.8
Surgery and chemotherapy	1	0.4
Radical radiotherapy	3	1.3
Chemotherapy	3	1.3
Palliative radiotherapy	24	1.3
None	192	84.6

All patients receiving potentially curative treatment lived more than a month, but three patients given palliative chemotherapy died within this time frame.

4) Factors affecting use of treatment

In order to explore the factors affecting whether or not patients received treatment, chi-squared and logistic regression analyses were performed (Table 3.7). There was no significant impact of gender or distance from cancer centre, but patients were less likely to receive treatment if they were older and lived in an area with an income below the median for British Columbia. As one would expect, treatment was also less frequently delivered to patients with metastatic disease and in those whom a pathological diagnosis had not been obtained.

Table 3.7 Factors affecting use of any treatment

ANY TREATMENT		Yes	No	χ^2	Unadjusted odds ratio of receiving treatment	Adjusted odds ratio of receiving treatment
Gender	Male	794 (65.3%)	421	P=0.34	1	1
	Female	578 (67.4%)	280		1.1 (0.9-1.3)	1.0 (0.8-1.3)
Age	<60	351 (82.8%)	73	**P<0.001**	1	1
	60-69	455 (72.7%)	171		**0.6 (0.4-0.8)**	**0.6 (0.4-0.9)**
	70-79	461 (62.7%)	274		**0.4 (0.3-0.5)**	**0.4 (0.3-0.6)**
	80+	105 (36.5%)	183		**0.1 (0.08-0.2)**	**0.2 (0.1-0.3)**
Distance to Cancer centre	<2 hrs	996 (67.4%)	481	P=0.07	1	1
	> 2 hrs	375 (63.1%)	219		0.8 (0.7-1.0)	0.8 (0.7-1.1)
Income CDN $	< 48,800	740 (63.5%)	425	**P<0.01**	1	1
	> 48,800	631 (69.6%)	275		**1.3 (1.1-1.6)**	**1.3 (1.1-1.7)**
Pathology Type	NSCLC	1081 (70.2%)	459	**P<0.001**	1	1
	SCLC	256 (83.7%)	50		**2.2 (1.6-3.0)**	**2.8 (1.9-3.9)**
	No pathology	35 (15.4%)	192		**0.07(0.05-0.1)**	**0.1 (0.1-0.2)**
Stage	Localised	390 (78.3%)	108	**P<0.001**	1	1
	Regional	429 (79.7%)	109		1.1 (0.8-1.5)	0.7 (0.5-1.0)
	Metastatic	490 (64.8%)	266		**0.5 (0.4-0.7)**	**0.4 (0.3-0.5)**
	Unknown	63 (22.4%)	218		**0.08 (0.06-1.1)**	**0.07 (0.05-0.11)**

Figures in bold are statistically significant ($p<0.05$)

i) Use of potentially curative treatment

Similarly patients were also more likely to be treated with curative intent if they were younger, lived in an area with a higher income, had NSCLC, and obviously if the disease was localised (Table 3.8).

Table 3.8 Factors affecting the use of potentially curative treatment

POTENTIALLY CURATIVE		Yes	No	χ^2	Unadjusted odds of receiving PCT	Adjusted odds ratio of receiving PCT
Gender	Male	313 (25.8%)	912	P=0.48	1	1
	Female	223 (27.2%)	625		1.1 (0.9-1.3)	1.0 (0.8-1.3)
Age	<60	134 (31.6%)	290	**P<0.001**	1	1
	60-69	189 (30.2%)	437		0.9 (0.7-1.2)	0.75 (0.53-1.08)
	70-79	199 (27.1%)	536		0.9 (0.6-1.0)	**0.62 (0.44-0.87)**
	80+	24 (8.3%)	264		**0.2 (0.1-0.3)**	**0.16 (0.09-0.27)**
Distance to Cancer centre	<2 hrs	377 (25.5%)	1110	P=0.19	1	1
	> 2 hrs	169 (28.5%)	425		1.2 (0.9-1.4)	1.1 (0.8-1.4)
Income CDN $	< 48,800	281(24.1%)	884	**P<0.01**	1	1
	> 48,800	264 (29.2%)	641		**1.3 (1.1-1.6)**	**1.4 (1.1-1.8)**
Pathology Type	NSCLC	466 (30.3%)	1074	**P<0.001**	1	1
	SCLC	72 (23.5%)	234		**0.7 (0.5-0.9)**	**2.1 (1.4-3-3.0)**
	No pathology	8 (3.5%)	219		**0.1 (0.04-0.2)**	**0.1 (0.04-0.2)**
Stage	Localised	296 (59.4%)	202	**P<0.001**	1	1
	Regional	202 (37.5%)	336		**0.4 (0.3-0.5)**	**0.27 (0.2-0.36)**
	Metastatic	12 (1.6%)	744		**0.01 (0.5-0.2)**	**0.01 (0-0.012)**
	Unknown	36 (12.8%)	245		**0.1 (0.07-0.15)**	**0.11 (0.07-0.16)**

5) Factors affecting delivery of surgery, radiotherapy of chemotherapy

i) Surgery

When deprivation was taken as a dichotomous variable (greater or less than Provincial median) then on chi-squared analysis only age, pathology type and stage affected the use of surgery; with younger patients with NSCLC and those with localised disease more likely to undergo a resection (Table 3.9). However, the very nature of surgery the stage and pathology type are more likely to be known so the logistic regression multivariate analysis without these variables, then only age over 70 years was significant.

However, if income was divided into six bands then surgery was more likely to be performed in patients below the age of eighty and in those living in areas with the highest average income levels (Table 3.10).

Table 3.10 Factors affecting the use of surgery (thorocotomy or resection) with income divided into five groups

		Number receiving treatment /total	χ^2	Unadjusted odds of surgery	Adjusted odds of surgery
Age	<60	117/424	P <0.001	1	1
	60-69	180/625		1.1(0.8-1.4)	1.1(0.8-1.4)
	70-79	175/735		0.8(0.6-1.1)	0.8 (0.6-1.1)
	80+	17/288		0.2(0.1-0.3)	**0.2(0.1-0.3)**
Income	<40K	79/409	P=0.053	1	1
	40-49K	198/799		1.4(1.03-1.8)	**1.5 (1.1-2.0)**
	50-59K	150/653		1.2(0.9-1.7)	1.3 (0.9-1.8)
	60-69K	43/156		1.6(1.04-2.4)	**1.9 (1.2-3.0)**
	70K+	19/54		2.3(1.2-4.2)	**2.5 (1.3-4.6)**

Age, gender, journey, income also entered into model

Table 3.9 Factors affecting the delivery of surgery radiotherapy and chemotherapy

	SURGERY*				RADIOTHERAPY				CHEMOTHERAPY			
	Number receiving this treatment	**χ^2 p value**	**Unadjusted odds ratio**	**Adjusted odds ratio**	**Number receiving this treatment**	**χ^2 p value**	**Unadjusted odds ratio**	**Adjusted odds ratio**	**Number receiving this treatment**	**χ^2 p value**	**Unadjusted odds ratio**	**Adjusted odds ratio**
Male Female	276 (23%) 213 (25%)	0.27	1 1.1 (0.9-1.4)	1 1.2 (0.9-1.4)	496(41%) 340 (40%)	0.62	1 1.0(0.8-1.1)	1 0.9(0.8-1.1)	206 (19%) 161 (17%)	0.32	1 1.1(0.9-1.4)	1 1.0(0.7-1.3)
<60 yrs 60-69 70-79 80+	117 (28%) 180 (29%) 175 (24%) 17 (6%)	<0.001	1 1.1 (0.8-1.4) 0.8 (0.6-1.1) **0.2 (0.1-0.3)**	**1** 1.1 (0.7-1.4) 0.8 (0.6-1.1) **0.2 (0.1-0.3)**	221 (52%) 268 (43%) 267 (36%) 80 (29%)	**<0.001**	1 **0.7(0.5-0.9)** **0.5(0.4-0.7)** **0.4(0.3-0.5)**	1 0.9(0.7-1.1) **0.7 (0.5-0.9)** **0.7(0.5-0.9)**	132 (31%) 123 (20%) 96 (13%) 16 (6%)	**<0.001**	1 **0.5(0.4-0.7)** **0.3(0.2-0.4)** **0.1(0.07-0.2)**	1 **0.3 (0.2-0.5)** **0.2 (0.1-0.3)** **0.07 (0.04-0.15)**
<2 hrs >2 hrs	337 (23%) 152 (26%)	0.19	1 0.9 (0.7-1.2)	1 0.9 (0.7-1.2)	635 (43%) 201 (34%)	**<0.001**	1 **1.4 (1.2-1.8)**	1 **1.3 (1.1-1.5)**	265 (18%) 102 (17%)	0.73	1 0.9(0.7-1.2)	1 1.0(0.7-1.3)
< 48,800 > 48,800	263 (23%) 226 (23%)	0.21	1 1.1 (0.9-1.4)	1 1.1 (0.9-1.4)	450 (39%) 386 (43%)	0.07	1 1.2 (1.0-1.4)	1 1.1(0.9-1.4)	178 (15%) 188 (21%)	**0.001**	1 **1.5(1.2-1.8)**	1 **1.5 (1.1-2.1)**
NSCLC SCLC No path	472 (31%) 3 (4%) 6 (3%)	<0.001	**1** **0.1 (0.05-0.2)** **0.06(0.0-0.15)**		694 (42%) 160 (52%) 27 (12%)	**<0.001**	1 **1.5(1.2-1.9)** **0.2(0.1-0.3)**	1 1.1(0.8-1.4) **0.3(0.2-0.4)**	131 (9%) 231 (76%) 4 (2%)	**<0.001**	1 **32.6(23.8-44.7)** **0.2(0.1-0.5)**	1 **39.6 (27.2-57.7)** 0.4 (0.1-1.1)
Localised Regional Metastatic Unknown	289 (58%) 138 (26%) 25 (3%) 37 (13%)	<0.001	**1** **0.25(0.2-0.3)** **0.02 (0.0-0.04)** **0.1 (0.07-0.16)**		143 (29%) 307 (57%) 384 (51%) 2 (1%)	**<0.001**	1 **3.3(2.5-4.3)** **2.5(2.0-3.3)** **0.02 (0-0.07)**	1 **3.0 (2.3-4.0)** **2.5(1.9-3.2)** **0.02(0.01-0.1)**	19 (4%) 125 (23%) 197 (26%) 26 (9%)	**<0.001**	**1** **7.6(4.6-12.6)** **8.9(5.5-14.5)** **2.6(1.4-4.7)**	1 **2.4 (1.4-4.2)** **2.9 (1.7-4.9)** 1.5 (0.7-3.1)

* Resection or thorocotomy, NS =non-significant, Bold = significant with p value <0.05

ii) Radiotherapy

On multivariate analysis, patients were more likely to receive radiotherapy if they were younger, had more advanced disease, or had tissue confirmation. Similarly, those patients who lived under two hours journey time from a cancer centre were more likely to receive radiotherapy, probably a consequence of patients and doctors being deterred by the long journey for those living in remote areas (Table 3.9). Income had no impact whether examined as a dichotomous or categorical variable.

iii) Chemotherapy

On chi-squared and multi-variate analyses younger patients, especially those under the age of 60 years, those with SCLC, or more advanced disease were more likely to receive chemotherapy, as were patients with a higher household income (Table 3.9). This was also observed if income was entered into the model as categorical variable (adjusted odds $CDN70+ 6.1(2.7-13.8), 60-69K 2.2 (1.1-4.2) compared to income group <40K).

The reason for the impact of income on the use of chemotherapy and surgery was uncertain, but could have reflected more co-morbid disease in socially deprived patients, which precluded the safe delivery of chemotherapy or an operation.

6) Overall Survival

Exact date of diagnosis was not available for three patients so were removed from the survival analysis.

Using the Kaplan-Meier method for the analysis of survival for the complete cohort of 2253 patients the median survival was 6.2 months, with 33.7% alive at one year, 20.1% two years and 9.4% at five years.

For the 2070 patients who lived more than one day following diagnosis, the median survival was 7.4 months, with 55.3% of patients surviving six months, 36.7% one-year, 22.0% two-years and 10.3% five-years (figure 3.2a). As one would expect patients with more advanced disease had reduced survival, as did those without a tissue diagnosis. Neither household income (as dichotomous or categorical variable), nor journey time to a cancer centre, were associated with a difference in survival, but as has been seen in several other series, women had significantly longer survival (Table 3.11 and figures 3.2b-e). Younger patients also had improved survival.

Figure 3.2a

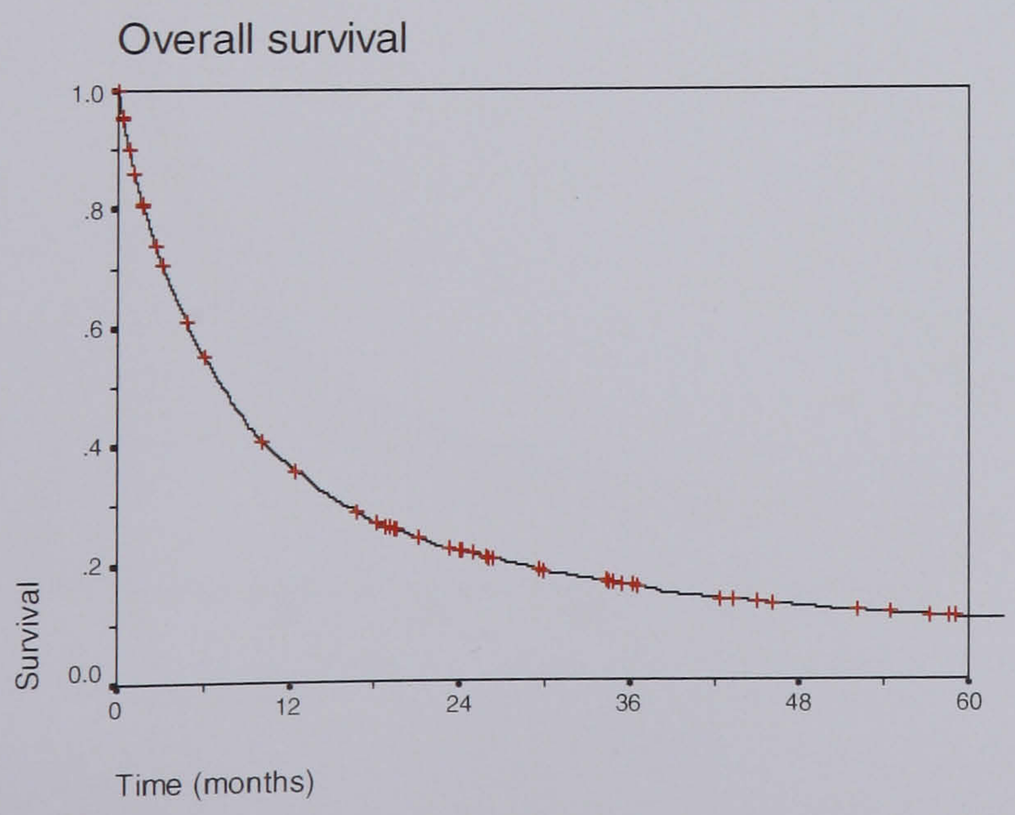
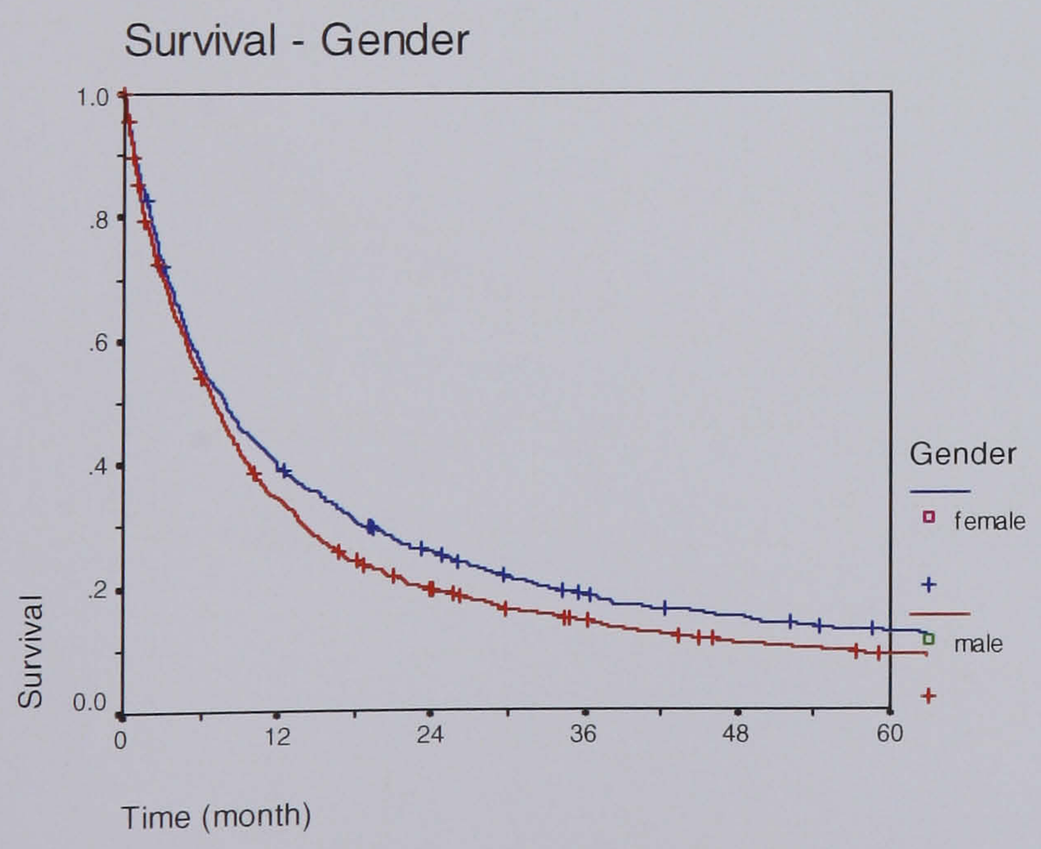


Table 3.11 Factors affecting survival of patients with lung cancer in BC 1995

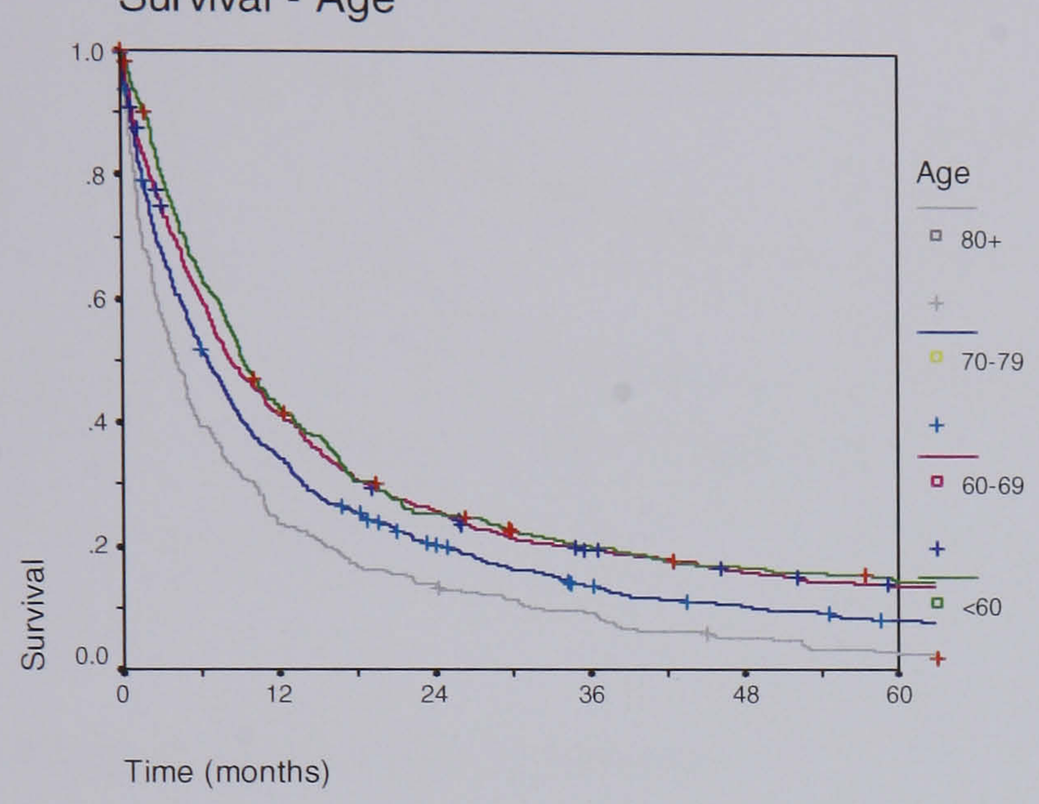
N=2070		Median survival (months)	Log rank	Unadjusted hazard of death	Adjusted hazard of death
Gender	Male	7.1 (6.4.7.8)	**P<0.001**	1	1
	Female	7.9 (6.8-9.0)		**0.9(0.8-0.9)**	**0.9 (0.8-0.9)**
Age	<60	9.4 (8.2-10.6)	**P<0.001**	1	1
	60-70	8.3 (6.9-9.6)		1.1(0.9-1.2)	1.1 (1.0-1.3)
	70-80	6.6 (5.7-7.5)		**1.3(1.2-1.5)**	**1.4 (1.2-1.6)**
	80+	4.0 (3.1-4.9)		**1.8(1.5-2.1)**	**1.6 (1.4-1.9)**
Income CDN $	<48,800	7.2 (6.5-8.0)	P=0.28	1	1
	>48,800	7.6 (6.7-8.5)		0.95(0.9-1.0)	(0.9-1.1)
Journey	<2 hr	7.1 (6.4-7.8)	P=0.26	1	1
	>2 hr	7.8 (6.8-8.9)		0.9 (0.8-1.0)	1.0(0.9-1.1)
Pathology	NSCLC	8.2 (7.4-9.0)	**P<0.001**	1	1
	SCLC	7.6 (6.6-8.7)		**1.4(1.2-1.6)**	1.0 (0.8-1.1)
	No pathology	2.7 (1.9-3.5)		**2.1(1.8-2.4)**	**1.7 (1.5-2.0)**
Stage	Localised	22.9 (19.2-26.6)	**P<0.001**	1	1
	Regional	10.9 (17.5-21.3)		**1.8(1.6-2.0)**	**1.9 (1.7-2.2)**
	Metastatic	3.7 (3.3-4.1)		**4.1(3.6-4.7)**	**4.3 (3.8-4.9)**
	Unknown	2.8 (2.1-3.6)		**3.0(2.6-3.6)**	**2.7 (2.3-3.2)**

Figure 3.2b



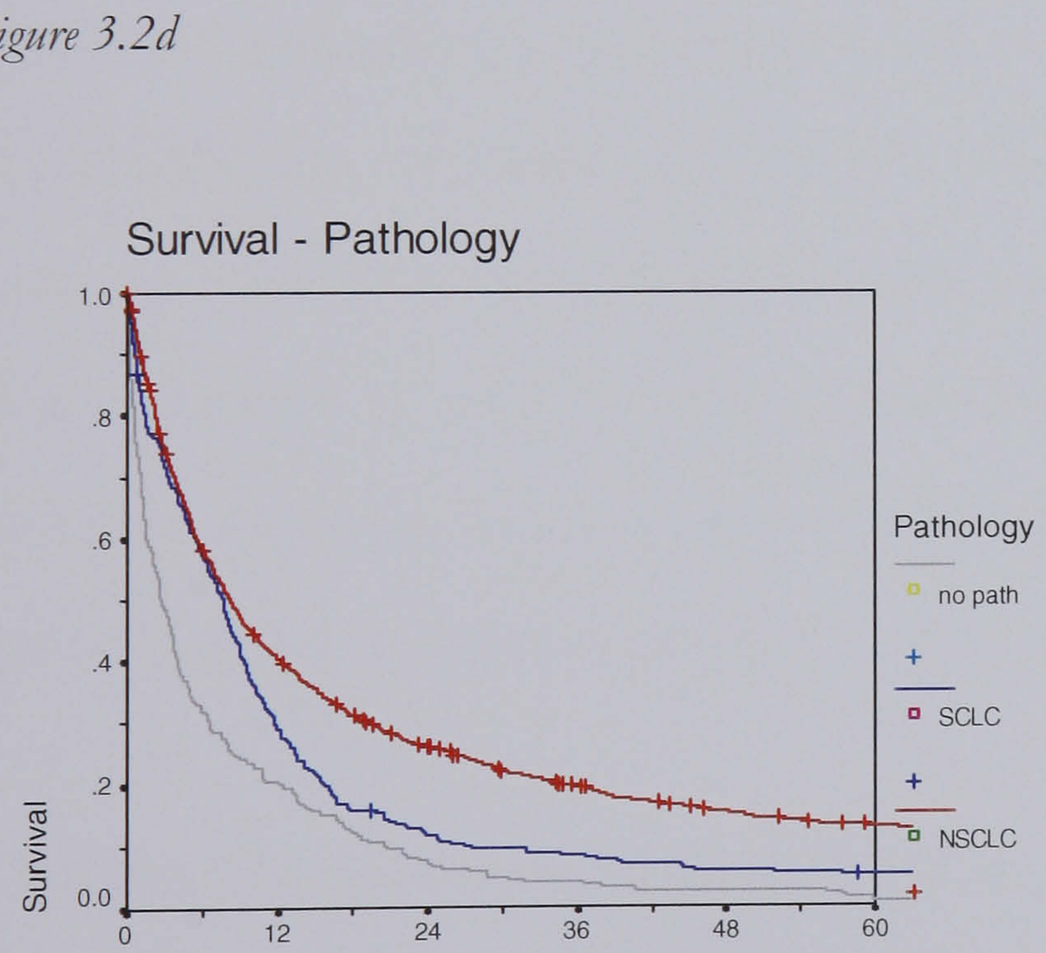
p<0.001

Figure 3.2c



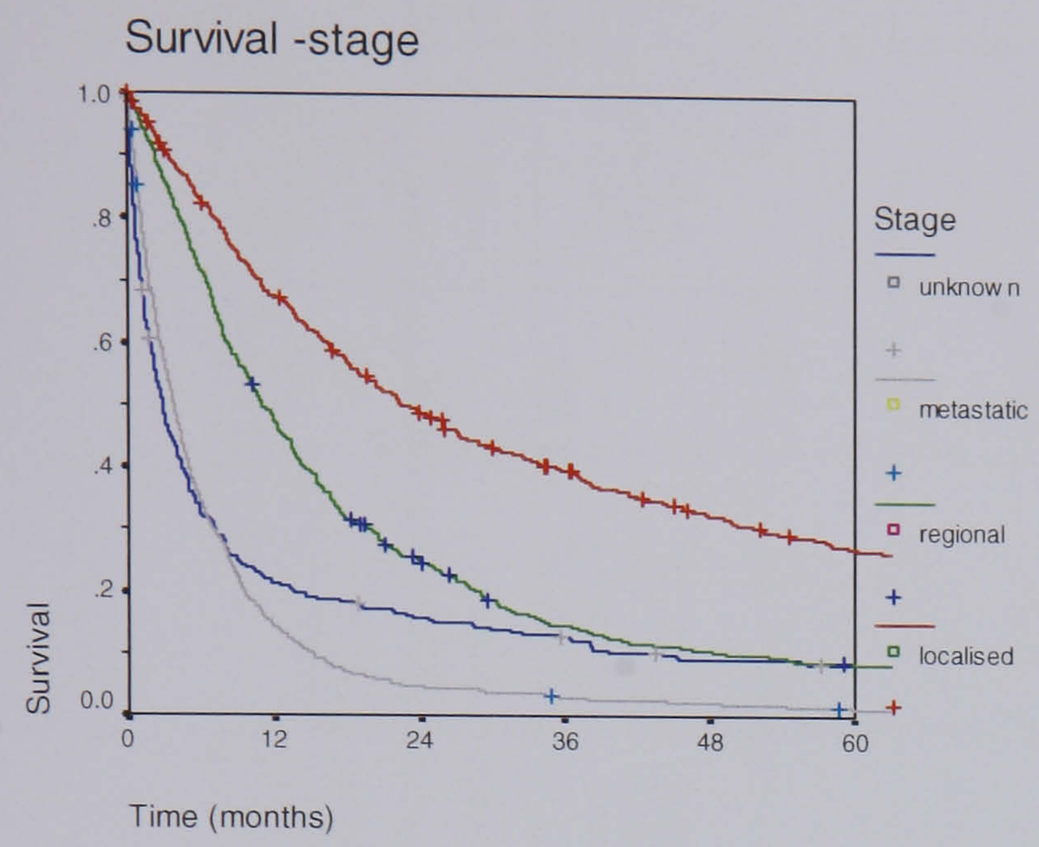
p<0.001

Figure 3.2d



p<0.001

Figure 3.2e



p<0.001

i) Overall survival and treatment

546 patients in the cohort received potentially curative treatment and had a median survival of 34 months (95%CI 29.4-38.5), 825 received palliative treatment only and had a median survival of 6.3 months (5.8-6.8) and 698 no treatment with a median survival of 2.3 months (2.1-2.8). The survival statistics for i) the different types of potentially curative therapy are shown in Table 3.12, ii) the factors affecting survival according to treatment intent are shown in Table 3.13, and iii) by treatment modality in Table 3.14. This analysis shows that regardless of treatment intent women had improved survival, as did younger patients, those with pathological confirmation, and with less advanced disease.

Table 3.12 Overall survival following potential curative therapy by treatment modality

	Median (months)	1 year	2 year	5 year
Resection n=438	40.8	81.0%	65.7%	38.6%
Radical radiotherapy (n=45)	17.6	68.2%	38.6%	10.6%
Limited SCLC chemo + radiation or surgery (n=72)	15.4	65.3%	35.9%	17.2%

Table 3.13 Overall survival and treatment intent

	ANY TREATMENT (N=1371)				POTENTIALLY CURATIVE (N=546)				NO TREATMENT (N=698)			
	Median survival (months)	Log rank P value	Unadjusted hazard of death	Adjusted Hazard of death	Median survival (months)	Log rank P value	Unadjusted hazard of death	Hazard ratio of death	Median survival (months)	Log rank	Unadjusted hazard of death	Hazard ratio of death
Male Female	9.6 (8.7-10.5) 10.9 (9.5-12.4)	**0.005**	1 **0.8(0.7-0.9)**	1 **0.9 (0.8-0.99)**	29.2 (23.1-35.3) 41.2 (31.8-50.5)	**0.003**	**1** **0.7(0.6-0.9)**	1 **0.8 (0.6-0.96)**	2.3 (1.7-3.0) 2.6 (2.1-3.1)	0.16	1 0.9(0.8-1.0)	1 **0.8 (0.7-0.98)**
<60yrs 60-70 70-80 80+	10.3 (8.7-12.0) 10.9 (8.8-12.9) 9.8 (8.3-11.4) 7.3 (5.9-8.8)	**<0.001**	1 1.0(0.8-1.1) 1.1(1.0-1.3) **1.5(1.2-1.9)**	1 1.0 (0.9-1.2) **1.3 (1.1-1.5)** **1.8 (1.4-2.2)**	40.2 (26.7-53.6) 38.8 (27.6-50.0) 27.8 (21.8-33.7) 30.7 (22.6-38.7)	**0.004**	1 1.0(0.8-1.3) **1.5(1.1-1.9)** **1.4(0.9-2.4)**	1 1.0 (0.8-1.4) **1.5 (1.2-2.0)** **1.6 (1.0-2.7)**	3.9 (1.8-3.6) 2.7 (1.8-5.7) 2.1 (1.7-2.5) 2.4 (1.9-3.0)	**0.02**	1 1.2(0.9-1.6) **1.5(1.1-1.9)** 1.3(1.0-1.7)	1 1.6 (0.9-1.5) **1.5 (1.1-1.9)** 1.2 (0.9-1.6)
<48,800 >48,800	9.7 (8.8-10.6) 10.5 (9.0-12.0)	0.82	1 1.0(0.9-1.1)	1 0.9(0.8-1.05)	37.7 (32.1-43.3) 28.2 (21.2-35.1)	0.24	1 1.1(0.9-1.4)	1 1.1 (0.9-1.3)	3.4 (2.0-2.7) 2.7 (1.9-3.4)	0.84	1 1.0(0.9-1.2)	1 1.0(0.9-1.2)
<2 hr >2 hr	9.7 (8.9-10.5) 11.6 (9.8-13.6)	0.13	1 0.9(0.8-1.0)	1 1.0(0.9-1.1)	33.0 (27.6-38.4) 37.2 (28-46.4)	0.67	1 1.0(0.8-1.2)	1 1.0 (0.8-1.3)	2.3 (1.9-2.8) 3.0 (2.2-3.7)	0.81	1 0.9(0.8-1.1)	1 0.9(0.7-1.0)
NSCLC SCLC No path	11.0 (9.7-12.3) 8.9 (7.9-9.8) 3.7 (1.9-5.4)	**<0.001**	1 **1.4(1.3-1.7)** **2.2(1.6-3.2)**	1 0.9 (0.8-1.1) **1.9 (1.3-2.7)**	37.9 (32.4-43.3) 15.4 (13.5-17.3) 14.2 (0-31.7)	**<0.001**	1 **1.9(1.4-2.5)** 1.8(0.8-3.9)	1 1.3 (0.9-1.7) 1.7 (0.8-3.7)	2.9 (2.3-3.4) 0..7 (0.4-0.98) 2.5 (1.8-3.2)	**<0.001**	1 **2.8 (2.1-3.8)** **1.2 (1.02-1.4)**	1 **2.5 (1.9-3.4)** **1.3 (1.1-1.6)**
Localised Regional Metastatic Unknown	32.3 (26.4-38.5) 12.3 (10.9-13.7) 5.0 (4.5-5.5) 9.2 (0-19.4)	**<0.001**	1 **2.0(1.7-2.4)** **4.9(4.2-5.7)** **1.6-1.2-2.2)**	1 **2.1 (1.8-2.5)** **5.1 (4.3-6.0)** **1.6 (1.2-2.2)**	48.5 (38.8-58.2) 20.2 (16.4-24.0) 13.7 (0-44.3) 44.1 (22.6-65.1)	**<0.001**	1 **2.0(1.6-2.5)** **2.8(1.5-5.3)** 1.3(0.8-1.9)	1 **1.9 (1.5-2.5)** **2.1 (1.1-4.0)** 1.2 (0.8-1.9)	12.1 (7.3-16.8) 6.1 (4.2-8.0) 1.4 (1.1-1.6) 2.0 (1.5-2.5)	**<0.001**	1 **1.3(1.01-1.7)** **2.6(2.0-3.3)** **1.9(1.5-2.4)**	1 **1.4 (1.1-1.9)** **2.7 (2.2-3.5)** **2.0 (1.6-2.5)**

Table 3.14 Overall survival and treatment type

	RESECTION* (N=438)[1]				RADIOTHERAPY (N=836)				CHEMOTHERAPY (N=367)			
	Median survival months	Log rank P value	Unadjusted hazard of death	Adjusted Hazard ratio death	Median survival months	Log rank P value	Unadjusted hazard of death	Adjusted Hazard ratio death	Median survival months	Log rank P value	Unadjusted hazard of death	Adjusted Hazard ratio death
Male Female	37.1 (30.3-43.9) 49.1 (36.4-61.9)	**0.02**	1 **0.8(0.6-0.98)**	1 0.8(0.6-1.05)	7.5 (6.8-8.3) 7.7 (6.7-8.8)	0.17	1 0.9(0.8-1.0)	1 0.9(0.8-1.1)	9.0 (8.1-9.8) 9.1 (7.7-10.6)	0.08	1 0.8(0.7-1.02)	1 0.8(0.7-10.2)
<60yrs 60-69 70-79 80+	57.3 (38.0-76.6) 45.8 (33.6-57.9) 36.8 (31.7-41.9) 27.3 (18.3-36.2)	**0.02**	1 1.1(0.8-1.5) **1.5(1.1-2.1)** 1.5(0.7-3.0)	1 1.1 (0.8-1.5) **1.6 (1.2-2.2)** 1.5 (0.7-3.0)	8.0 (7.1-8.8) 7.7 (6.7-8.8) 7.0 (5.9-8.2) 7.1 (5.2-9.1)	**<0.001**	1 0.9(0.6-1.1) 1.1(0.9-1.2) 1.1(0.9-1.5)	1 1.0 (0.8-1.2) 1.2 (1.01-1.5) 1.3 (1.02-1.7)	9.4 (8.5-10.3) 9.3 (7.5-11.2) 9.1 (7.5-10.5) 6.9 (5.3-8.6)	0.05	1 0.9(0.7-1.2) 1.1(0.8-1.4) **1.9(1.1-3.2)**	1 0.8 (0.6-1.04) 1.0(0.8-1.4) **2.9 (1.6-5.0)**
<2 hrs > 2 hrs	40.2 (33.2-47.1) 41.3 (30.3-52.2)	0.98	1 1.0(0.8-1.3)	1 1.0(0.8-1.3)	7.5 (6.9-8.1) 8.2 (7.1-9.3)	0.24	1 0.9(0.8-1.1)	1 0.9(0.8-1.1)	8.2 (7.0-9.3) 9.1 (8.2-10.0)	0.12	1 1.2(1.0-1.5)	1 1.2(1.0-1.6)
< 48,800 > 48,000	41.2 (34.8-47.7) 39.3 (25.9-52.8)	0.76	1 1.0(0.8-1.3)	1 1.0(0.8-1.3)	7.4 (6.7-8.2) 7.8 (6.8-8.8)	0.41	1 0.9(0.8-1.1)	1 0.9(0.8-1.1)	8.7 (7.6-9.6) 9.4 97.9-10.8)	0.19	1 0.9(0.7-1.1)	1 1.0(0.8-1.2)
NSCLC SCLC No path	41.3 (35.2-47.3) 22.3 (0-73.3) 22.2 (0-55.5)	0.13	1 0.9(0.4-2.2) 2.4(1.0-5.8)	1 0.5(0.2-1.3) 2.1(0.9-5.4)	7.0 (6.4-7.7) 10.4 (8.7-12.1) 3.6 (3.1-4.1)	**<0.001**	**1** **0.7(0.6-0.9)** **1.8(1.2-2.7)**	**1** **0.6 (0.5-0.8)** **1.6 (1.05-2.3)**	8.6 (7.8-9.7) 9.4 (8.4-10.4) 1.6 (0-4.3)	0.34	1 1.1(0.8-1.2) 2.0(0.8-5.6)	1 1.1(0.8-1.4) 0.9(0.3-2.8)
Localised Regional Metastatic Unknown	53.6 (43.1-64.1) 26.9 (20.1-33.7) 13.6 (0-44.0) 44.1 (22.6-65.5)	**<0.001**	1 **1.8(1.4-2.4)** **3.1(1.6-5.9)** 1.4(0.9-2.1)	1 **2.0 (1.5-2.6)** **2.3 (1.2-4.4)** 1.3 (0.8-2.0)	11.1 (8.7-13.6) 10.6(9.0-12.1) 4.8 (4.3-5.2) 4.6 (n=2)	**<0.001**	1 1.1(0.9-1.4) **2.5(2.0-3.0)** **4.4(1.1-17.7)**	**1** **1.4 (1.1-1.7)** **3.0 (2.4-3.7)** **3.6 (0.8-15.1)**	10.1(7.4-12.9) 13.3(10.5-16.1) 7.9 (7.1-8.8) 4.3 (2.16.5)	**<0.001**	1 1.0(0.6-1.6) **2.0(1.2-3.4)** **3.2(1.7-5.9)**	1 0.9(0.5-1.5) **2.0 (1.2-3.4)** **3.0 (1.5-6.1)**

* Pneumonectomy, lobectomy or segmentectomy.

[1] There was difference in survival for those surgeons operating on ≥ 30 cases or <30 cases.

ii) Cause specific survival

As discussed in Chapter 2 for patients with a diagnosis of lung cancer cause specific analysis should be taken with caution.

By five years, of the original 2073 patients, 1651 (80%) had died of lung cancer, 183 died of other causes and 239 were alive. Survival rates, as calculated by the Kaplan Meier method are shown in Table 3.15. (For data on relative survival see Chapter 5)

Table 3.15 Cause specific survival and treatment intent and pathological type

	Median (months)	1 year	2 year	5 year
Whole group (n=2070)	8.2 (7.5-8.8)	39.9%	25.0%	13.9%
Potentially curative treatment (n=546)	40.6 (32.9-48.3)	80%	63.9%	42.7%
Palliative treatment (n=826)	6.6 (6.1-7.1)	24.4%	8.7%	2.6%
No treatment (n=698)	2.0 (2.5-3.6)	26.1%	12.8%	3.0%
NSCLC (n=1540)	9.0 (8.1-9.9)	43.4%	28.2%	17.1%
SCLC (n=306)	7.9 (6.9-8.8)	30.5%	12.9%	6.1%
No pathology (n=224)	3.7 (2.7-4.6)	28.0%	11.3%	2.0%

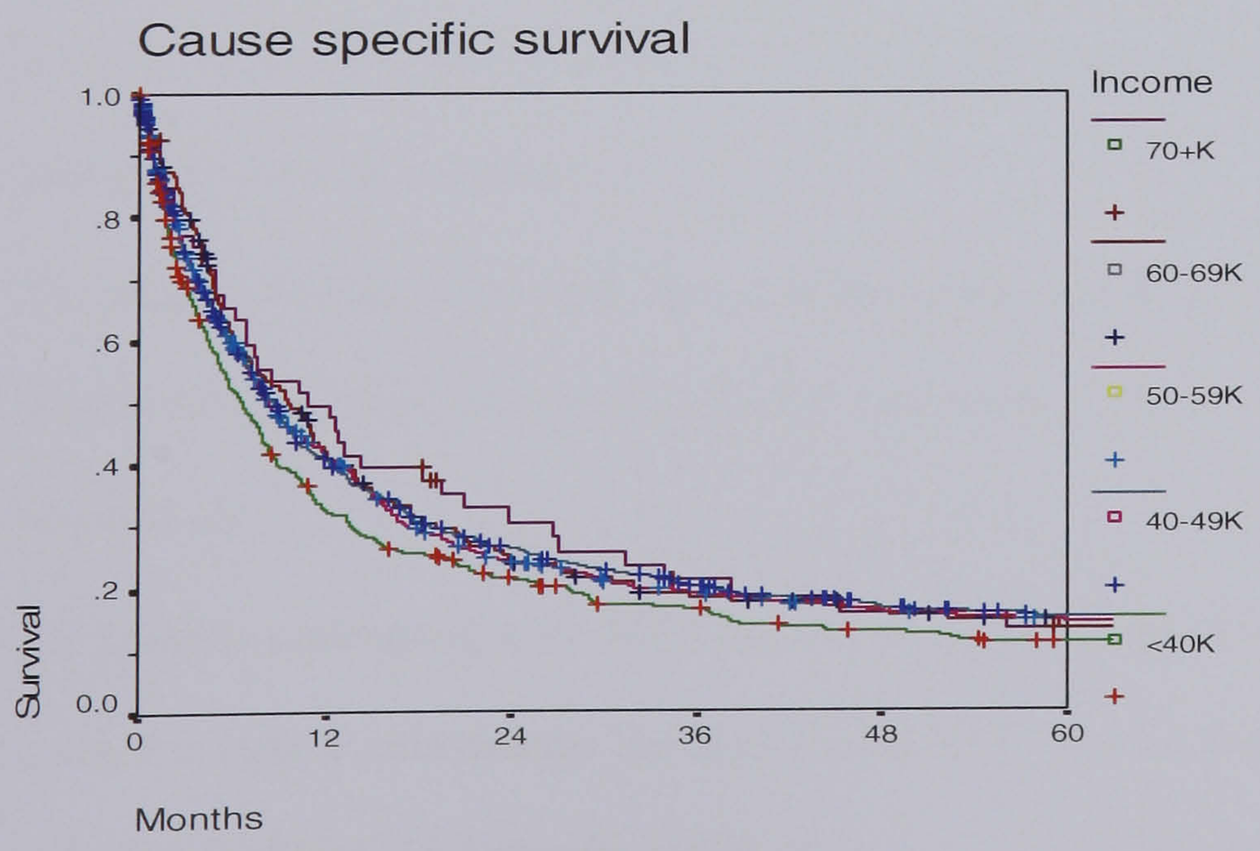
In the Cox's regression model gender, age over 70, no pathology, and more advanced disease all predicted for increased hazard of dying of lung cancer (Table 3.15).

Table 3.15 Factors affecting cause specific survival

		Median (months)	Log rank P value	Unadjusted hazard of lung cancer death	Adjusted hazard of lung cancer death
Gender	Male	7.9 (7.2- 8.6)	**0.009**	1	1
	Female	8.8 (7.5-10.0)		**0.9(0.8-0.96)**	**0.9 (0.8-0.96)**
Age	<60	9.7 (8.2-11.2)	**0.001**	1	1
	60-69	9.8 (8.2-11.4)		1.0(0.9-1.1)	1 (0.9-1.2)
	70-79	7.6 (6.6-8.6)		**1.2(1.1-1.4)**	**1.4 (1.2-1.6)**
	80+	4.8 (3.8-5.9)		**1.6(1.4-1.9)**	**1.5 (1.3-1.8)**
Distance	< 2 hours	8.0 (7.3-8.7)	0.23	1	1
	> 2 hours	8.4 (7.2-9.7)		0.9(0.8-1.0)	1.0(0.9-1.1)
Income CDN	< 48,800	7.9 (7.2-8.7)	0.25	1	1
	> 48,000	8.5 (7.3-9.7)		0.9(0.8-1.0)	1.0(0.9-1.1)
Pathology Type	NSCLC	9.0 (8.1-9.9)	**0.001**	1	1
	SCLC	7.9 (6.9-8.8)		**1.4(1.3-1.6)**	1 (0.9-1.1)
	No pathology	3.7 (2.7-4.6)		**1.9(1.7-2.3)**	**1.6 (1.4-1.9)**
Stage	Localised	29.7 (23.0-36.3)	**0.001**	1	1
	Regional	11.9 (10.4-13.4)		**2.1(1.8-2.4)**	**2.2 (1.9-2.6)**
	Metastatic	4.0 (3.6-4.4)		**4.8(4.2-5.5)**	**5.0 (4.4-5.8)**
	Unknown	3.6 (2.5-4.7)		**3.2(2.7-3.8)**	**2.9 (2.4-3.5)**

When income was examined as a categorical variable then there was a trend for improved survival for patients in the highest income group (figure 3.3 Log rank p=0.063)

Figure3.2 Cause specific survival by income group



p=0.063

Summary of results

- 2256 patients diagnosed with lung cancer in 1995 of whom 59% were male.
- The pathological confirmation rate was 83%, with 34% adenocarcinoma, 26% squamous cancer, 16% small cell, 12% large cell and 12% other types of NSCLC.
- 22% of patients had localised disease, 24% regional, 33.5% metastatic and 12.5% stage was unknown. 8% were diagnosed either at autopsy or on day of diagnosis and so were excluded from treatment analysis.
- Of the remaining 2073 patients, 26% were treated with curative intent, 40% received palliative treatment and 34% received no treatment.
- The resection rate was 19% of the whole population, with the 438 resections performed by 25 different surgeons
- 41% of the population received radiotherapy for their lung cancer, but only 2% of the population received radical radiotherapy
- 17.3% of the population received chemotherapy, 75.5% of SCLC cases and 8.6% NSCLC
- Patients were more likely to receive treatment if they were younger, lived in a more affluent area or had loco-regional disease. The traveling time to the closest cancer centre had no influence on whether or not the patient received treatment. The same factors also affected the delivery of potentially curative treatment.
- The median overall survival for the complete cohort was 6.2 months and for the group of 2073 who lived more than one day the survival rates were 37%, 22% and 10.3% at 1, 2 and 5 years respectively.
- For patients undergoing a resection the median survival was 40.8 months with 39% alive at five years, for radical radiotherapy the figures were 17.6 months and 10.6%, and following chemo-radiation for SCLC 15.4 months and 17.2%.

CHAPTER 4

Lung Cancer in Scotland in 1995: treatment and survival

Methods

The Scottish Cancer Registry was one of the first cancer registries to be setup and achieved national coverage in 1959. Cases are identified from a variety of sources, such as pathology reports, hospital discharge summaries, cancer centre databases, and death certificates. The case ascertainment is one of the highest in the world with more than 96.5% of cancer cases being identified [25]. Due to the methods of case identification it is likely that the ascertainment for lung cancer is actually higher than this; though no specific data exist.

A retrospective audit was conducted in 1998 of all cases of lung cancer diagnosed in 1995 identified by the Scottish Cancer Registry. A three-month window either side was allowed to ensure complete data capture. Specially employed audit staff manually examined all the patients' medical records.

Though the data on general patient characteristics, treatment and outcome have been published [83], along with a more detailed paper on chest radiotherapy [62], the detailed data on chemotherapy and surgery have not been published.

For the purposes of this study a complete re-analysis of the data has been performed using the following variables:

Name

Gender

Date of birth

Postcode

Date of diagnosis – defined in order of priority as date of pathological diagnosis, date of radiological diagnosis, date of clinical diagnosis

Method of diagnosis (pathology, cytology, autopsy, radiological, clinical)

Pathological type

Staging investigations (CT scans, bronchoscopy)

Site of tumour

Stage of tumour defined as localised, regional or metastatic

Treatment received within six months of diagnosis (except adjuvant radiotherapy following chemotherapy for limited stage SCLC as this can start during the seventh month).

Date of death – this was originally linked to the death registry at the end of 1998, but for the purposes of this study, a second linkage up to the end of 2002 was performed.

Derived variables

To enable comparison with the BC data the same variables were derived. Namely:

1) Age at diagnosis - grouped into four categories aged under 60, 60-69, 70-79, and over 80 years.

2) Distance to cancer centre – in British Columbia a two-hour journey is considered socially acceptable, but in Scotland work performed by the Scottish Executive Health Department suggests that a one-hour journey is preferable. Therefore, for the

comparison a further variable 'socially acceptable journey' i.e. two hours for Canada and one hour for Scotland was used.

3) Income and deprivation – the Carstairs deprivation index has been developed for Scotland and uses four factors (overcrowding, male unemployment, social class 4 and 5 and car ownership) to calculate a score for each post-code, which is then divided into five or seven categories (1= least deprived and 7 = most deprived) [36] . The seven categories do not divide the Scottish population evenly; 6% of Scottish population reside in an area in category 1 - 14%; 2 - 22%; 3 -25%; 4 -15%; 5 -11%; 6 - 6%; category 7 - 7%. As the only index of deprivation for BC was median income, the Scottish population was also split into two groups, which roughly equate to half the Scottish population; those Carstairs index 1-3 (42%) and those Carstairs index 4-7 (58%)[128].

4) Summary pathology - the following groups were formed: small cell, non-small cell and no pathology.

5) Staging – when the original data was collected a system of localised, regional and metastatic stage was used corresponding to localised to lung, spread to regional lymph node and distant metastases, respectively. However for some cases, where the TNM stage was available, this did not appear to always to concur, therefore for these cases the staging was amended so node negative NSCLC patients had 'Localised' disease, N1 or N2 NSCLC patients and Limited stage SCLC 'Regional' disease, and M1 NSCLC ,and Extensive stage SCLC 'Metastatic' disease.

6) Potentially curative therapy – this was defined as for the BC patients.

7) Palliative treatment - this was defined as for the BC patients.

8) Chemotherapy – the regimens were combined to form two groups; multiple agents or single agent /unknown regime.

9) Survival time – time from date of diagnosis to date of death or date of censorship (31/12/2002)

10) Cause of death – the primary and secondary cause of death were available. Those patients with lung cancer as primary cause of death or with lung cancer as secondary cause of death but an obvious association, for example pneumonia, were defined as having died of lung cancer. Other causes of death were combined to form a single group of patients with 'other cause of death'.

Analysis

An analysis similar to that conducted for British Columbia was performed.

Results

1) Patient and tumour characteristics

The Scottish Cancer Registry identified 4465 people diagnosed with lung cancer. The following were excluded from the audit; 115 diagnosed or treated outside Scotland, 79 not primary lung cancer, 18 an incidental finding at autopsy, 18 other reasons. Of the 4225 potentially eligible cases, 370 had to be excluded because of inadequate medical records (including 102 death certificate only), leaving 3855 cases in the study (91.2% eligible cases). Of these 87 had the date of diagnosed recorded as either the end of 1994, for 28 at the beginning of 1996.

Of the 3855 cases, 2341 (60.7%) were men, and the median age was 70 (range 34-97). Only 57 (6.7%) lived more than one hour's journey from a cancer centre. The distribution of the deprivation categories is shown in Table 4.1. As one would predict, more cases occurred in more deprived areas.

Table 4.1 Distribution of deprivation in the seven categories

Carstairs Index	1	2	3	4	5	6	7
Number	141	393	734	988	649	556	394
%	3.7	10.2	19.0	25.6	16.8	14.4	10.2

The diagnosis was confirmed with histology in 51.6% cytology 20.1% (ante-mortem pathological confirmation rate of 71.7%). In 1456 (37.8%) cases, the tumour was located in the upper lobes, 719 (18.7%) the lower lobes, 142 (3.7%) right middle lobe, 390 (10.1%)

main bronchus or trachea, 263 (6.9%) more than one site and in 885 (23.0%) the site was unknown.

Of the 2856 (74.1%) patients with pathological confirmation, 557 (19.5%) had adenocarcinoma, 1106 (38.7%) squamous cell, 678 (23.7%) small-cell, 180 (6.3%) large cell, 256 (9%) NSCLC–NOS, and 79 (2.8%) were found to have other pathological types. The pathological diagnosis was not obtained in 999 patients. For the purposes of analysis three groups NSCLC, SCLC and no pathology were formed. There were some differences in the gender and travel times for these pathological groups (χ^2 with $p<0.05$), but not deprivation index (Table 4.2)

Table 4.2 Distribution of gender and travel times for the three pathological groups

		NSCLC	SCLC	No pathology
Gender	Male	1414 (64.9%)	356 (52.2%)	571 (57.2%)
	Female	764 (35.1%)	322 (47.5%)	428 (42.8%)
Journey	< 1hour	1984 (91.1%)*	625 (92.2%)	914 (91.5%)
	> 1 hour	161 (7.4%)	37 (5.5%)	59 (5.9%)

* Remaining patients did not have post-code recorded

Staging information was available for 89.2% of the cases, with 964 (25.2%) of whole cohort presenting with localised disease, 32.7% regional, and 31.4% metastases.

2) Treatment

As the patients with a 'death-certificate-only' diagnosis had been excluded from the original audit there were only 22 cases in this cohort where the date of diagnosis was the same as the date of death. These were excluded from the treatment analysis, leaving 3833 cases.

i) Any treatment

Of the 3833 patients, 548 (14.3%) received potentially curative treatment, 1638 (42.7%) palliative and 1647 (43%) no treatment.

ii) Surgery

443 patients (11.6%) of patient underwent an attempted resection, for 37 patients (8.3% of operations or 1% population) this was an 'open-shut' thorocotomy, and for 406 (10.6%) a cancer resection was performed.

The majority of operations were performed in men (63%), with a median age of 64 (range 34 to 82), only 8.6% lived more than one hour from a cancer centre and 37.1% of cases lived more affluent areas.

Lobectomy was the most frequently performed resection, with 224 (5.8%) patients undergoing this type of operation, with 160 (4.2%) having a pneumonectomy and 22 (0.6%) a segmentectomy or wedge resection. Forty patients died (9.0% of operations) within a month of their operation, giving a 14.4% post-operative mortality rate for pneumonectomy, 5.8% for lobectomy and 8% for 'open and shut' thoracotomy. These rates are higher than most other published series from this period [51].

The pathological subtypes were as follows; squamous cell 215 cases (48.5% operations) 144 adenocarcinoma, 28 large cell, 43 NSCLC NOS and 13 SCLC.

The detailed pathological stage (TNM 1997) for all the cases that underwent an attempted resection is shown in Table 4.3.

Table 4.3 The distribution of pathological staging groups

N=443	IA	IB	IIA	IIB	IIIA	IIIB	IV	LI	NOT RECORDED
Number	58	105	16	75	42	8	6	13	120
%	13.1	23.7	3.6	16.9	9.5	1.8	0.7	2.9	27.1%

Table 4.4 includes the 406 resected tumours according to the more general staging and type of resection performed

Table 4.4 Distribution of general stage by operation type

N=406	Localised (n)	Regional (n)	Metastatic (n)
Segmentectomy	18	4	0
Lobectomy	160	63	1
Pneumonectomy	66	92	2

Thirty-six patients with NSCLC received post-operative radiotherapy, 31 with a dose of greater than 40Gy. Most of these cases had stage IIB disease (41.7%) or IIIA disease (30.6%). Four patients received palliative radiotherapy within six months. Forty-two patients who had surgery also received chemotherapy within the first six-months after diagnosis. Of

the 13 operated SCLC cases, two received adjuvant radiotherapy and chemotherapy, and four received chemotherapy alone.

ii) Radiotherapy

1400 (36.5%) of patients received radiotherapy in the first six months following diagnosis (including chemoradiation for SCLC). The first course of treatment consisted of radical radiotherapy with a dose of ≥50Gy for 94 patients (2.5% population, 3.0% of those with NSCLC or no pathology), pre- or post-operative radiotherapy 36 (0.9% population), adjuvant thoracic treatment or prophylactic cranial irradiation (PCI) for SCLC 58 (1.5% population, 8.6% SCLC), palliative radiotherapy to the chest 1028 (26.8% population) and palliative radiotherapy elsewhere 184 (4.8% population).

Forty-four patients had a radiotherapy intent described as 'radical', but the dose delivered was less than 50Gy (median 40Gy range 30-45) so the treatment was defined in this study as palliative. For the patients receiving radical radiotherapy the median dose was 52.5Gy (range 50-60Gy), using a median of 20 fractions (range 20-30). For the 50 SCLC patients who received adjuvant thoracic radiotherapy, the median dose was 40Gy (range 30-50) using a median of 15 fractions (range 9-20).

For the 1220 patient who underwent palliative radiotherapy, 225 (18.5%) died within a month of starting this treatment.

iii) Chemotherapy

Chemotherapy was delivered to 621 patients, 16.2% of the population. For those with SCLC, 425 (63.1%) received chemotherapy (79.3% with a combination of agents) whereas only 178 (8.4%) patients with NSCLC received chemotherapy (49% combination chemotherapy) and 18 (1.8%) patients with no pathology (56% combination chemotherapy). Eighty (13%) of the patients receiving chemotherapy died within a month of starting chemotherapy, 66 of whom had SCLC.

3) Treatment combinations by pathological groups

i) Small Cell Lung Cancer

There were 674 patients with SCLC, of whom 52% had limited stage disease. However, only 36% had a CT scan performed so there could be under detection of metastatic disease.

The treatment combinations are shown in Table 4.5

Table 4.5 Treatment delivered patients with SCLC

	Number	%
Surgery* only	5	0.7
Surgery* and chemotherapy	4	0.6
Surgery*, chemotherapy and post operative radiotherapy	2	0.3
Chemotherapy and PCI (no thoracic radiotherapy)	8	1.2
Chemotherapy and adjuvant thoracic radiotherapy	48	7.1
Chemotherapy	312	46.3
Chemotherapy and palliative radiotherapy	51	7.6
Palliative radiotherapy	71	10.5
None	173	25.7

* = Resection

For the 351 patients with limited-stage disease 59 (16.8%) received potentially curative therapy (surgery +/- chemotherapy or chemoradiation), 5 chemotherapy and PCI only, 224 (63.8%) palliative treatment (chemotherapy and/or radiotherapy) and 63 no treatment. Therefore, 252 (71.8%) of limited stage patients received chemotherapy.

For the 286 extensive stage patients, 151 (52.8%) received chemotherapy (+/- palliative radiotherapy), 35 had palliative radiotherapy alone, and 100 had no record of any treatment.

There were 37 unstaged patients of whom 22 (59.4%) were treated with chemotherapy (+/- radiotherapy), 5 radiotherapy alone, and 10 had no treatment.

As stated earlier, 32 patients with extensive stage SCLC who received chemotherapy, but died within a month of diagnosis, a 21% first cycle death rate. For the limited stage patients 31 died (12%) within a month, and three unstaged patients. These rates are higher than other series from this era, when first cycle mortality rates of 10% for extensive stage disease and 5% for limited staged were observed in clinical trials

ii) Non-Small Cell Lung Cancer

A total of 2168 patients were diagnosed with pathologically confirmed NSCLC. A CT scan was performed in 59% of this group of patients. Localised disease was present in 36%, 32% regional, 26% metastatic, and for 6% the stage was unknown.

The distribution of management is shown in Table 4.5.

Table 4.5 Treatment delivered patients with NSCLC

	Number	%
Surgery* only	315	14.5
Surgery* and chemotherapy	40	1.8
Surgery*, chemotherapy and post operative radiotherapy	1	0.1
Surgery*, chemotherapy and palliative radiotherapy	1	0.1
Surgery* and post operative radiotherapy	35	1.6
Surgery* and radical radiotherapy	0	0
Surgery* and palliative radiotherapy	3	0.1
Radical radiotherapy	77	3.6
Radical radiotherapy and chemotherapy	2	0.1
Palliative radiotherapy	808	37.3
Chemotherapy	95	4.4
Chemotherapy and palliative radiotherapy	39	1.8
None	752	34.7

* = Resection

Potentially curative treatment (primary treatment surgery or radical radiotherapy) was used in 21.9% of patients, 43.4% received palliative treatment and 34.7% no treatment. Table 4.6 demonstrates the management intent broken down by the extent of disease. The differences shown are statistically significant (χ^2 with $p<0.001$).

Table 4.6 Intent of treatment broken down by extent of disease

	Localised	Regional	Metastatic	Unknown	Total
potentially curative	298	168	7	1	474
	38.9%	24.2%	1.2%	0.7%	21.9%
palliative	263	331	305	43	942
	30.5%	47.7%	53.5%	31.4%	43.5%
none	206	195	258	93	752
	26.9%	28.1%	45.3%	67.9%	34.7%
Total	797	694	570	137	2168

338 patients died within a month of diagnosis. Forty patients died within a month of surgery (9%) (37 after a resection and three after a thoracotomy), 141 within a month of starting palliative radiotherapy and 12 (7%) died one month after first dose of chemotherapy.

iii) Patients without pathological confirmation

A total of 991 patients did not have a pathological diagnosis. Localised disease was present in 19.9% of cases, regional in 21.1%, metastatic in 34.9% and the stage was unknown for 24%. A CT scan was performed in 33% of this group of patients.

The management is shown in Table 4.7.

Table 4.7 Treatment delivered patients without pathological confirmation

	Number	%
Radical radiotherapy	15	1.5
Chemotherapy and palliative radiotherapy	3	0.3
Chemotherapy	15	1.5
Palliative radiotherapy	236	23.8
None	722	72.9

A total of 337 of these patients died within a month. Fifty-nine died within a month of starting palliative radiotherapy and two after palliative chemotherapy.

4) Factors affecting use of treatment

In order to explore which factors affected whether or not patients received treatment chi-squared and logistic regression multi-variate analyses were performed (see Table 4.8). Patients were more likely to receive treatment if they were younger, had loco-regional disease, had SCLC, lived in a more affluent area, or lived **further** than one hour's drive from a cancer centre.

Table 4.8 Univariate and multivariate analysis of factors affecting the delivery of 'any treatment'

ANY TREATMENT		Yes	No	χ^2 p value	Unadjusted odds ratio	Adjusted odds ratio
Gender	Male	1358 (59%)	969	**0.042**	1	1
	Female	828 (55%)	678		**0.9(0.8-0.99)**	0.9 (0.8-1.07)
Age	<60	466 (81%)	110	**<0.001**	1	1
	60-69	843 (67%)	416		**0.5(0.4-0.6)**	**0.52 (0.4-0.7)**
	70-79	743 (52%)	694		**0.25(0.2-0.3)**	**0.31 (0.2-0.4)**
	80+	134 (24%)	427		**0.07(0.05-0.1)**	**0.1 (0.08-0.15)**
Distance	<1 hour	1959 (56%)	1543	**<0.001**	1	1
	>1 hour	185 (72%)	71		**2.0(1.5-2.7)**	**2.1 (1.5-2.9)**
Deprivation	Cat 4-7	1432 (56%)	1140	**0.017**	1	1
	Cat 1-3	754 (60%)	507		**1.2(1.03-1.4)**	**1.3 (1.1-1.5)**
Pathology	NSCLC	1416 (65%)	752	**<0.001**	1	1
	SCLC	501 (74%)	173		**1.5(1.3-1.9)**	**1.8 (1.4-2.2)**
	No pathology	268 (27%)	722		**0.2(0.17-0.23)**	**0.3 (0.3-0.4)**
Stage	Localised	614 (64%)	350	**<0.001**	1	1
	Regional	877 (70%)	377		**1.3(1.1-1.6)**	1.0 (0.8-1.2)
	Metastatic	606 (50%)	596		**0.6(0.5-0.7)**	**0.5 (0.5-0.6)**
	Unknown	89 (22%)	324		**0.15(0.1-0.2)**	**0.26 (0.17-0.31)**

i) The effect of health board and region on treatment delivery

In the previous publication by Erridge *et al* [62], it was noted that healthboard of diagnosis affected the use of treatment. Therefore an additional chi-squared additional analysis was conducted which included healthboard and is shown in Table 4.9. The differences observed were statistically significant (χ^2 p <0.001).

Table 4.9 Proportion of patients receiving 'any treatment' by healthboard of diagnosis

HB	1	2	3	4	5	6	7	8	9	10	11	12	13
Yes	4	113	107	543	95	176	106	54	162	439	37	94	256
(%)	(25)	(45.6)	(49.1)	(50.7)	(52.8)	(54)	(55.2)	(56.3)	(58.7)	(64.4)	(69.8)	(70.7)	(74.9)
No	12	135	111	528	85	150	86	42	114	243	16	39	86

For simplicity, and to allow comparison with current practice, the Health Boards were placed into three regions, which now form the three Scottish Cancer Networks; West of Scotland (WOSCAN), East of Scotland (SCAN) and North of Scotland (NOSCAN) (though these were not in existence in 1995). Patients living in Region 3 (NOSCAN) and Region 2 were much more likely to receive treatment than those in Region 1 (WOSCAN) (χ^2 p<0.001 for both comparisons) (Table 4.10)

Table 4.10 Proportion of patients receiving 'any treatment' by 'Region'

Any treatment	Region 1 (WOSCAN) (HB 2,3,4,5,6)	Region 2 (SCAN) (HB 7,8,10,11)	Region 3 (NOSCAN) (HB 1, 9, 12,13)
Yes	1034 (50.6%)	636 (62.2%)	516 (67.3%)
No	1009	387	251

To investigate the potential reasons for this observation, the demographic characteristics for the three regions were examined and are shown in Table 4.11. Three–quarters of patients in

Region 1 lived in a deprived area compared with half the patients in Region 3. However, there were no differences in age or gender. However, pathological confirmation and staging was more common in Region 1 than Region 3.

Table 4.11 Distribution of patient and tumour related characteristics by 'Region'

		Region 1	Region 2	Region 3	χ^2
Gender	Male	1240 (60.7%)	603 (58.9%)	484 (63.1%)	P=0.20
	Female	803 (39.3%)	420 (41.1%)	283 (36.9%)	
Age	<60	305 (14.9%)	149 (14.6%)	122 (15.9%)	P=0.25
	60-69	700 (34.3%)	327 (32.0%)	232 (30.2%)	
	70-79	752 (36.8%)	401 (39.2%)	284 (37.0%)	
	80+	286 (14.0%)	146 (14.3%	129 (16.8%)	
Distance	<1 hr	1952 (97.4%)	938 (94.0%)	612 (81.1%)	**P<0.001**
	> 1 hr	53 (2.6%)	60 (6.0%)	143 (18.9%)	
Depriv'n	Cat 4-7	1604 (78.5%)	595 (58.2%)	373 (48.6%)	**P<0.001**
	Cat 1-3	439 (21.5%)	428 (41.8%)	394 (51.4%)	
Path	NSCLC	1117 (54.7%)	603 (59.3%)	444 (57.9%)	**P<0.001**
	SCLC	370 (18.1%)	183 (17.9%)	121 (15.8%)	
	No pathology	556 (27.2%)	233 (22.8%)	202 (26.3%)	
Stage	Localised	580 (28.4%)	265 (25.9%)	119 (15.5%)	**P<0.001**
	Regional	654 (32.0%)	346 (33.8%)	254 (33.1%)	
	Metastatic	641 (31.4%)	296 (28.9%)	265 (34.6%)	
	Unknown	168 (8.2%)	116 (11.3%)	129 (16.8%)	

Therefore, the variable 'Region' was also inserted into the logistic regression model examining the factors affecting the use of treatment. Distance to cancer centre, pathology type, stage and Region were all significant predictors of the use of treatment, but gender and income were no longer statistically significant (see Table 4.14). This suggests that it may be healthcare organisation and resources issues, rather than social deprivation that influenced the use of treatment.

5) Use of potentially curative treatment

The factors affecting the use of potentially curative treatment were examined in a multivariate analysis and are shown in Table 4.12. This demonstrated that younger patients, those with NSCLC or localised disease were more likely to receive potentially curative therapy.

Table 4.12 Univariate and multivariate analysis of factors affecting use of potentially curative treatment

POTENTIALLY CURATIVE		Yes	No	χ^2 p value	Unadjusted odds of PCT	Adjusted odds ratio Of PCT
Gender	Male	344 (15%)	1983	0.30	1	1
	Female	204 (14%)	1302		0.9(0.7-1.1)	1.1(0.8-1.3)
Age	<60	150 (26%)	426	**<0.001**	1	1
	60-69	257 (20%)	1002		**0.7(0.6-0.9)**	**0.7 (0.4-0.8)**
	70-79	136 (10%)	1301		**0.3(0.2-0.4)**	**0.25(0.2-0.35)**
	80+	5 (1%)	556		**0.03(0.01-0.06)**	**0.03 (0.01-0.07)**
Distance	<1 hour	494 (14%)	3008	**0.038**	1	1
	>1 hour	49 (19%)	207		**1.4(1.04-2.0)**	1.4(0.9-2.1)
Depriv'n	Cat 4-7	359 (14%)	2213	0.40	1	1
	Cat 1-3	189 (15%)	1072		1.1(0.9-1.3)	1.1(0.9-1.4)
Pathology	NSCLC	474 (22%)	1694	**<0.001**	1	1
	SCLC	59 (9%)	615		**0.35(0.25-0.45)**	**0.6 (0.4-0.8)**
	No pathology	15 (2%)	976		**0.05(0.03-0.1)**	**0.1 (0.07-0.2)**
Stage	Localised	309 (32%)	655	**<0.001**	1	1
	Regional	229 (18%)	1025		**0.5(0.4-0.6)**	**0.4 (0.3-0.5)**
	Metastatic	9 (1%)	1193		**0.02(0.01-0.03)**	**0.02 (0.01-0.03)**
	Unknown	1 (0.2%)	412		**0.01(0.0-0.04)**	**0.01 (0.01-0.07)**

The model was then repeated to include the new variable 'Region' and age, pathology type and stage remained significant predictors as did 'Region' of residence (Odds ratios compared to Region1, Region 2 0.99 (NS) Region 3 1.66 (CI 1.25-2.2, p=0.001)), but the differences seen were smaller than for the use of any treatment.

6) Factors affecting delivery of surgery, radiotherapy or chemotherapy

i) Surgery

On chi-squared analysis the only factors affecting use of surgery were age, pathology type and stage. With younger patients, those with NSCLC, or localised disease more likely to have had a resection (see Table 4.13).

As discussed in the analysis of the Canadian patients, there is a potential issue that the extra information gained by surgery may bias the analysis, so it was performed with and without pathology and stage. When all the variables were used age, stage and pathology were significant predictors of having operation, as was deprivation with odds of undergoing surgery of 1.28 for the least deprived compared with the most deprived group (p=0.045). However, when pathology and stage were removed from the model only age and social deprivation remained significant factors; possibly reflecting increased co-morbidity with increasing age and poverty [128].

If pathology and stage were kept, and the variable 'Region' added to the model then age, stage, pathology type, and also 'Region' were significant, with the odds of undergoing surgery 1.6 (1.2-2.2) for Region 3 compared with Region 1 (p=0.003). However, when Region 2 was compared with Region 1 the difference was non-significant. If the variables pathology and stage were then removed 'Region of diagnosis' was no longer a significant factor affecting the use of surgery with age and social deprivation the only factors affecting the use of surgery (Table 4.14).

ii) Radiotherapy

On chi-squared analysis, patients were more likely to receive radiotherapy if they were younger, had NSCLC, regional disease, if they were male, or they lived further from a cancer centre (see Table 4.13). However, on multivariate analysis gender was no longer a significant factor for receiving radiotherapy, and only age, traveling time, pathology, and stage remained significant.

Then, if the variable Region was added to the model traveling time was no longer a significant factor, but there was a significantly higher chance of receiving radiotherapy in Region 2 (OR 1.9 (1.6-2.3) $p<0.001$) and Region3 (OR 2.8 (2.7-3.4) $p<0.001$) when compared with Region 1 (Table 4.14). So, younger patients, those with NSCLC, those with mediastinal involvement, and patients living out-with Region 1 were most likely to have received radiotherapy.

iii) Chemotherapy

On chi-squared and multi-variate analyses younger patients, those with SCLC and regional stage disease were most likely to receive chemotherapy (see Table 4.13). The model did not change when the additional variable of 'Region' was added (Table 4.14).

Table 4.13 Univariate and multivariate analysis of factor affecting the delivery of the different treatment modalities

	SURGERY*				RADIOTHERAPY				CHEMOTHERAPY			
	Number (%)	χ^2 p value	Unadjusted odds ratio	Adjusted odds ratio	Number (%)	χ^2 p value	Unadjusted odds ratio	Adjusted odds ratio	Number (%)	χ^2 p value	Unadjusted odds ratio	Adjusted odds ratio
Male	279 (12)	0.3	1	1	891 (39)	**0.005**	**1**	1	358 (15)	0.045	1	1
Female	164 (11)		0.9(0.7-1.1)	1.0(0.8-1.1)	509 (34)		**0.8(0.7-0.9)**	0.9(0.8-1.04)	268 (18)		**1.2(1.01-1.4)**	1.0(0.8-1.3)
Age 60	125 (22)	**<0.001**	**1**	1	267 (46)	**<0.001**	1	**1**	184 (32)	**<0.001**	**1**	1
60-69	205 (16)		**0.7 (0.5-0.8)**	**0.7 (0.5-0.8)**	494 (39)		**0.7(0.6-0.9)**	**0.8 (0.6-0.9)**	258 (22)		**0.5(0.4-0.7)**	**0.5 (0.4-0.7)**
70-79	110 (8)		**0.3 (0.2-0.4)**	**0.3 (0.2-0.4)**	535 (37)		**0.7(0.5-0.8)**	**0.8 (0.6-0.9)**	165 (12)		**0.3(0.2-0.4)**	**0.2 (0.2-0.3)**
80+	3 (0.5)		**0.02 (0-0.1)**	**0.02 (0-0.1)**	111 (20)		**0.3(0.2-0.4)**	**0.4 (0.3-0.6)**	19 (3)		**0.1(0.05-0.12)**	**0.1 (0.0-0.1)**
<1 hr	402 (12)	0.11	1	1	1244 (36)	**<0.001**	1	1	575 (16)	0.12	1	1
>1hr	38 (15)		1.3(0.9-1.9)	1.2(0.9-1.8)	130 (51)		**1.9(1.5-2.4)**	**1.7 (1.3-2.3)**	32 (13)		0.7(0.5-1.1)	0.7(0.4-1.1)
Cat 4-7	279 (11)	0.053	1	1	915 (36)	0.087	1	1	425 (17)	0.68	1	1
Cat 1-3	164 (13)		1.3(1.0-15)	**1.3 (1.1-1.7)**	484 (39)		1.1(0.99-1.3)	1.1(0.95-1.3)	201 (16)		1.0(0.8-1.1)	1.1(0.9-1.4)
NSCLC	430 (20)	**<0.001**	1		966 (45)	**<0.001**	1	1	183 (8)	**<0.001**	1	1
SCLC	13 (2)		**0.01(0.0-0.1)**		180 (27)		**0.5(0.4-0.6)**	**0.4 (0.3-0.5)**	425 (63)		**19.1(15.3-23.8)**	**21.8 (16.7-28.4)**
No path	0		0		254 (26)		**0.45(0.4-0.5)**	**0.5 (0.4-0.7)**	18 (2)		**0.2(0.1-0.3)**	**0.4 (0.2-0.6)**
Localised	261 (27)	**<0.001**	1		354 (37)	**<0.001**	**1**	**1**	52 (5)		1	1
Regional	174 (14)		**0.5(0.4-0.6)**		537 (42)		**1.3(1.1-1.5)**	**1.5 (1.3-1.9)**	326 (26)	**<0.001**	**6.5(4.9-8.9)**	**1.9 (1.3-2.7)**
Metastatic	6 (0.5)		**0.02(0.01-0.03)**		443 (37)		**1.0(0.8-1.2)**	**1.3 (1.1-1.6)**	219 (18)		**4.1(3.0-5.7)**	1.1 (0.7-1.6)
Unknown	2 (0.5)		**0.01(0.0-0.05)**		66 (16)		**0.3(0.2-0.4)**	**0.5 (0.4-0.7)**	29 (7)		1.4(0.9-2.3)	1.1 (0.6-1.9)

* Resection or thoracotomy

Table 4.14 Multivariate analysis of factors (including 'Region') affecting the delivery of any treatment and different modalities

		ANY TREATMENT	PCT	SURGERY*	RADIOTHERAPY	CHEMOTHERAPY
		Adjusted odds ratio	Adjusted odds ratio	Adjusted odds ratio	Adjusted odds ratio	Adjusted odds ratio
Gender	Male	1	1	1	1	1
	Female	0.9(0.8-1.1)	1.1(0.8-1.3)	1.0(0.8-1.2)	0.9(0.8-1.03)	1.0(0.8-1.3)
Age	<60	1	1	1	**1**	1
	60-69	**0.5 (0.4-0.7)**	**0.6 (0.5-0.8)**	**0.7 (0.6-0.9)**	**0.8 (0.6-0.97)**	**0.5 (0.4-0.7)**
	70-79	**0.3 (0.2-0.4)**	**0.2 (0.2-0.4)**	**0.3 (0.2-0.4)**	**0.8 (0.6-0.9)**	**0.22 (0.17-0.3)**
	80+	**0.1 (007-0.15)**	**0.03 (0.01-0.07)**	**0.02 (0.01-0.07)**	**0.4 (0.3-0.5)**	**0.06 (0.04-0.11)**
Distance to Cancer centre	<1 hr	1	1	1	1	1
	>1hr	**1.5 (1.1-2.1)**	1.2(0.8-1.8)	1.2(0.8-1.8)	1.3(0.9-1.6)	0.7(0.4-1.2)
Region	1	1	1	1	**1**	1
	2	**1.8 (1.5-2.2)**	1.0 (0.8-1.3)	0.8(0.6-1.1)	**1.9 (1.6-2.3)**	0.9(0.8-1.2)
	3	**3.0 (2.4-3.7)**	**1.6 (1.2-2.2)**	1.0(0.8-1.4)	**2.8 (2.3-3.4)**	0.8(0.6-1.1)
Deprivation	Cat 4-7	1	1	1	1	1
	Cat 1-3	1.0(0.9-1.2)	1.1(0.9-1.4)	**1.4 (1.1-1.7)**	0.9(0.8-1.03)	1.2(0.9-1.5)
Pathology Type	NSCLC	1	1		**1**	1
	SCLC	**1.9 (1.5-2.4)**	**0.6 (0.4-0.9)**		**0.4 (0.3-0.5)**	**21.8 (16.7-28.4)**
	No pathology	**0.33 (0.27-0.4)**	**0.1 (0.7-0.2)**		**0.6 (0.5-0.7)**	**0.4 (0.2-0.6)**
Stage	Localised	1	1		**1**	1
	Regional	0.9 (0.7-1.1)	**0.4 (0.3-0.5)**		**1.4 (1.2-1.7)**	**1.9 (1.3-2.7)**
	Metastatic	**0.4 (0.3-0.5)**	**0.01 (0.0-0.03)**		1.2 (0.96-1.4)	1.1 (0.7-1.6)
	Unknown	**0.17 (0.12-0.23)**	**0.0 (0.0-0.07)**		**0.4 (0.3-0.5)**	1.0 (0.6-1.9)

6) Overall survival

The median overall survival was 3.6 months, with survival rate at one year 21.1%, two years 9.5% and five years 4.9%. The Kaplan Meier plot is shown in Figure 4.1.

Figure 4.1

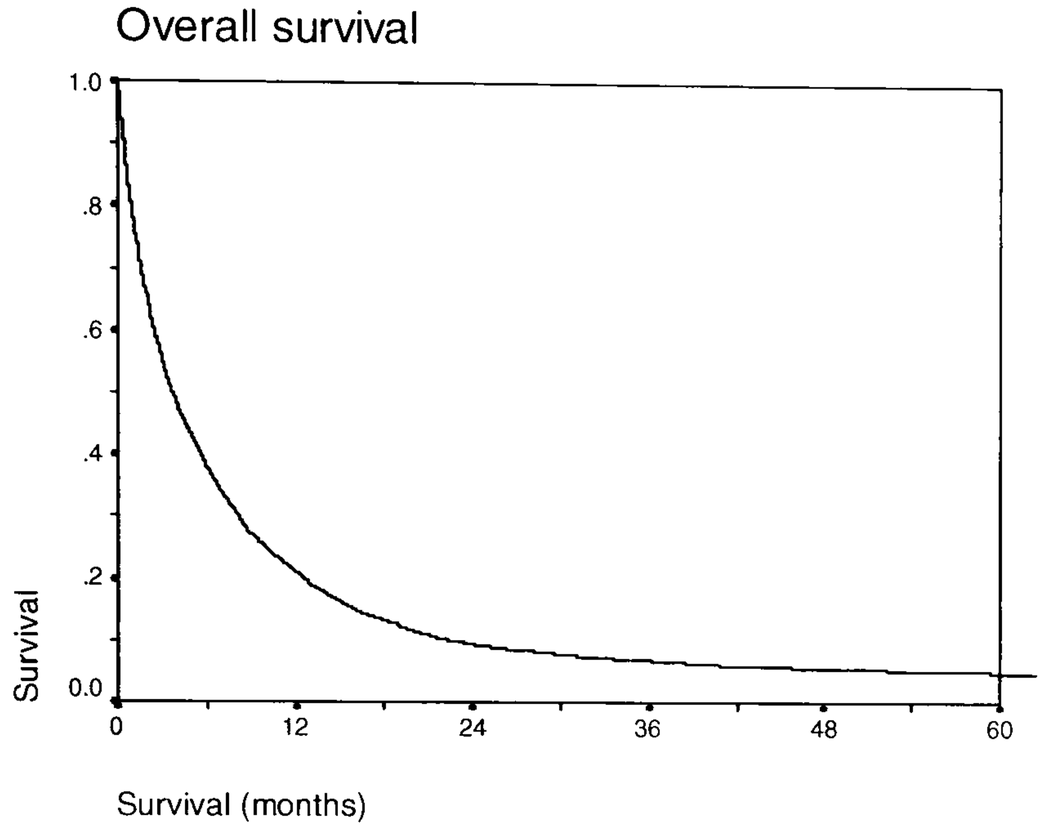
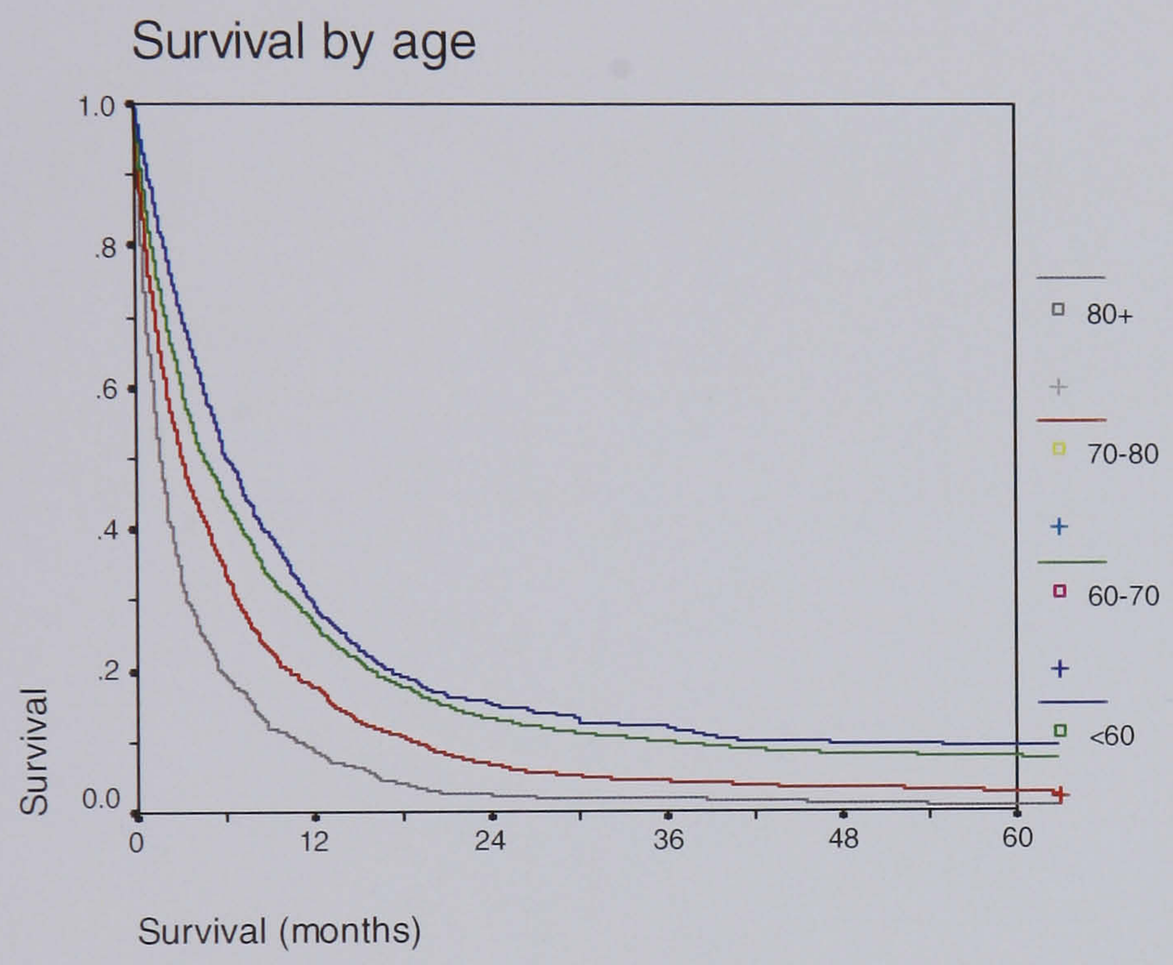


Table 4.15 Factors affecting overall survival

		Median survival (months)	Log rank P value	Unadjusted hazard of death	Adjusted hazard of death
Gender	Male	3.6 (3.3-3.9)	0.29	1	1
	Female	3.6 (3.2-4.0)		0.96(0.9-1.03)	**0.9 (0.8-0.96)**
Age	<60	6.1 (5.3-6.8)	**<0.001**	1	1
	60-70	4.7 (4.1-5.2)		**1.2(1.04-1.3)**	**1.2 (1.1-1.3)**
	70-80	3.2 (2.8-3.5)		**1.6(1.4-1.7)**	**1.6(1.5-1.8)**
	80+	1.6 (1.4-1.9)		**2.3(2.1-2.6)**	**2.3 (2.0-2.6)**
Distance to Cancer centre	<1 hr	3.5 (3.2-3.7)	**<0.001**	1	1
	>1hr	5.4 (4.1-6.7)		**0.8(0.7-0.9)**	**0.8 (0.7-0.96)**
Deprivation	Cat 4-7	3.5 (3.2-3.8)	**0.008**	1	1
	Cat 1-3	4.0 (3.5-4.4)		**0.9(0.85-0.98)**	**0.9 (0.8-0.95)**
Pathology	NSCLC	5.1 (4.6-5.5)	**<0.001**	1	1
	SCLC	3.7 (3.1-4.3)		**1.4(1.3-1.5)**	1.1 (0.98-1.2)
	No pathology	2.0 (1.7-2.2)		**1.9(1.8-2.1)**	**1.4(1.3-1.6)**
Stage	Localised	8.2(7.3-9.2)	**<0.001**	1	1
	Regional	5.4 (4.9-6.0)		**1.5(1.4-1.7)**	**1.6(1.4-1.7)**
	Metastatic	2.0 (1.8-2.2)		**3.2(2.9-3.6)**	**3.4 (3.1-3.7)**
	Unknown	1.5 (1.2-1.9)		**3.0(2.6-3.3)**	**2.3(2.1-2.6)**

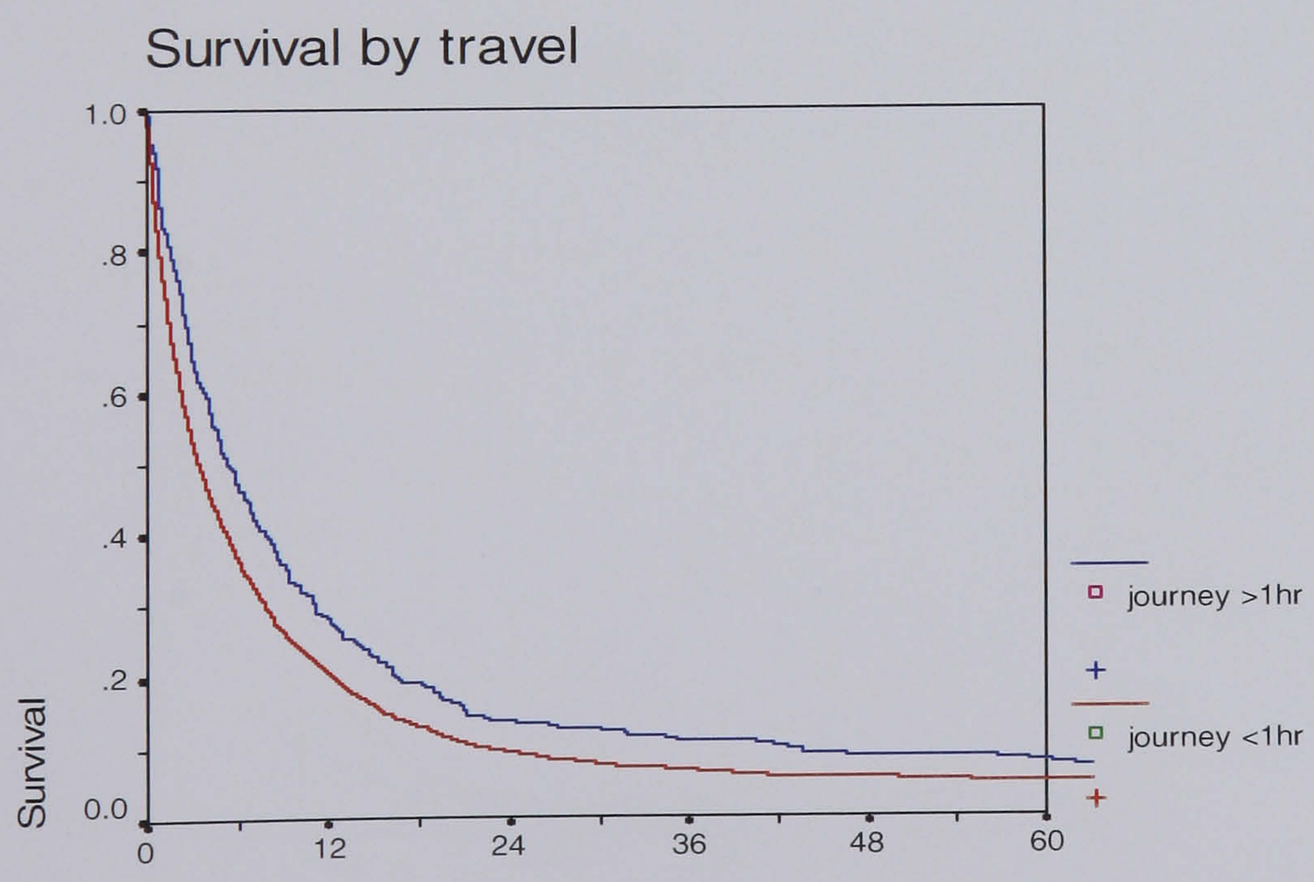
On log rank analysis younger age, living in a less deprived area, a longer traveling distance were all associated with improved survival, along with NSCLC pathology and localised disease (Table 4.15 and figures 4.2a-e). In a multivariate analysis male gender was associated with an increased risk of death, but SCLC was not.

Figure 4.2a



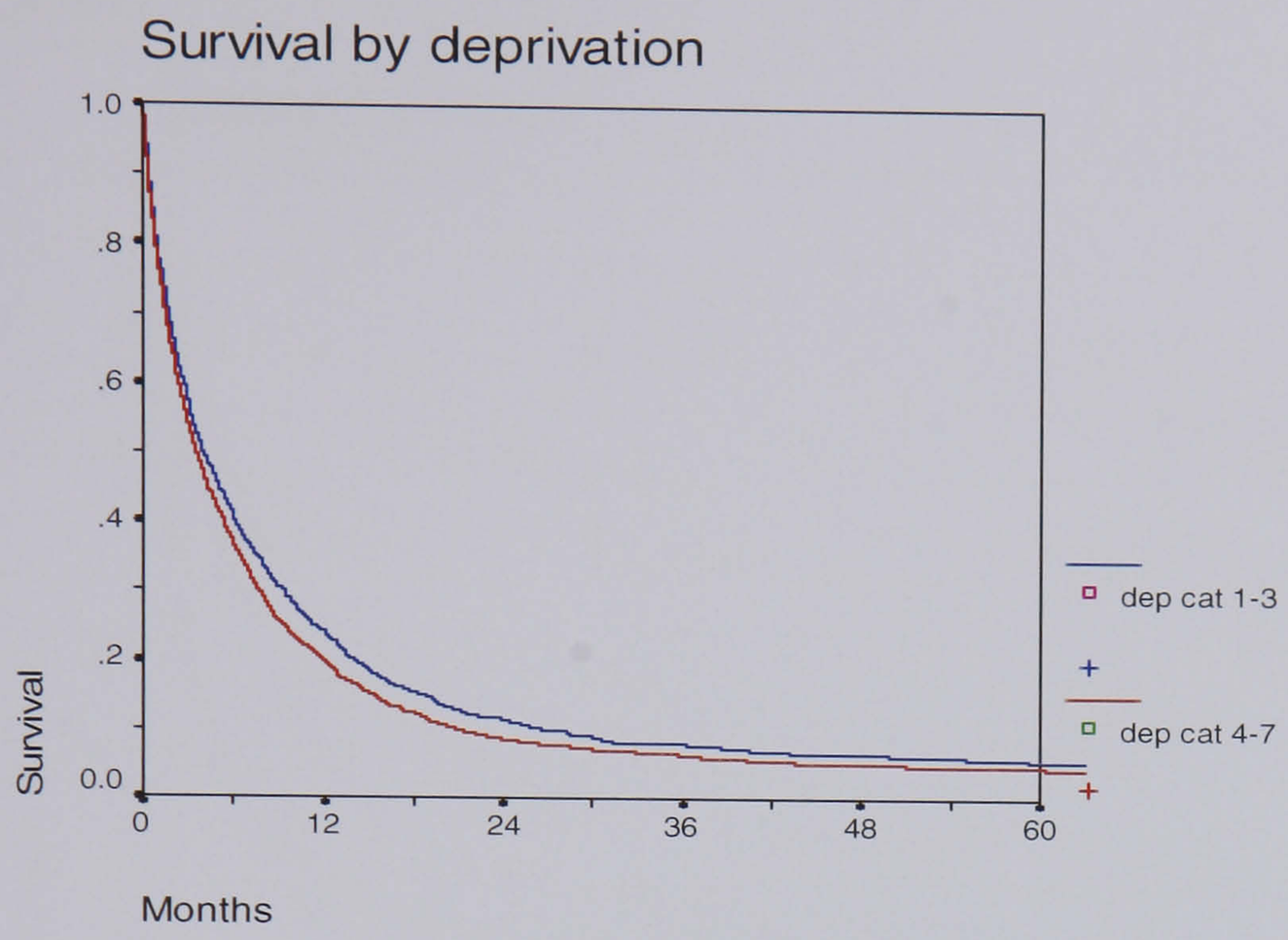
p<0.001

Figure 4.2b



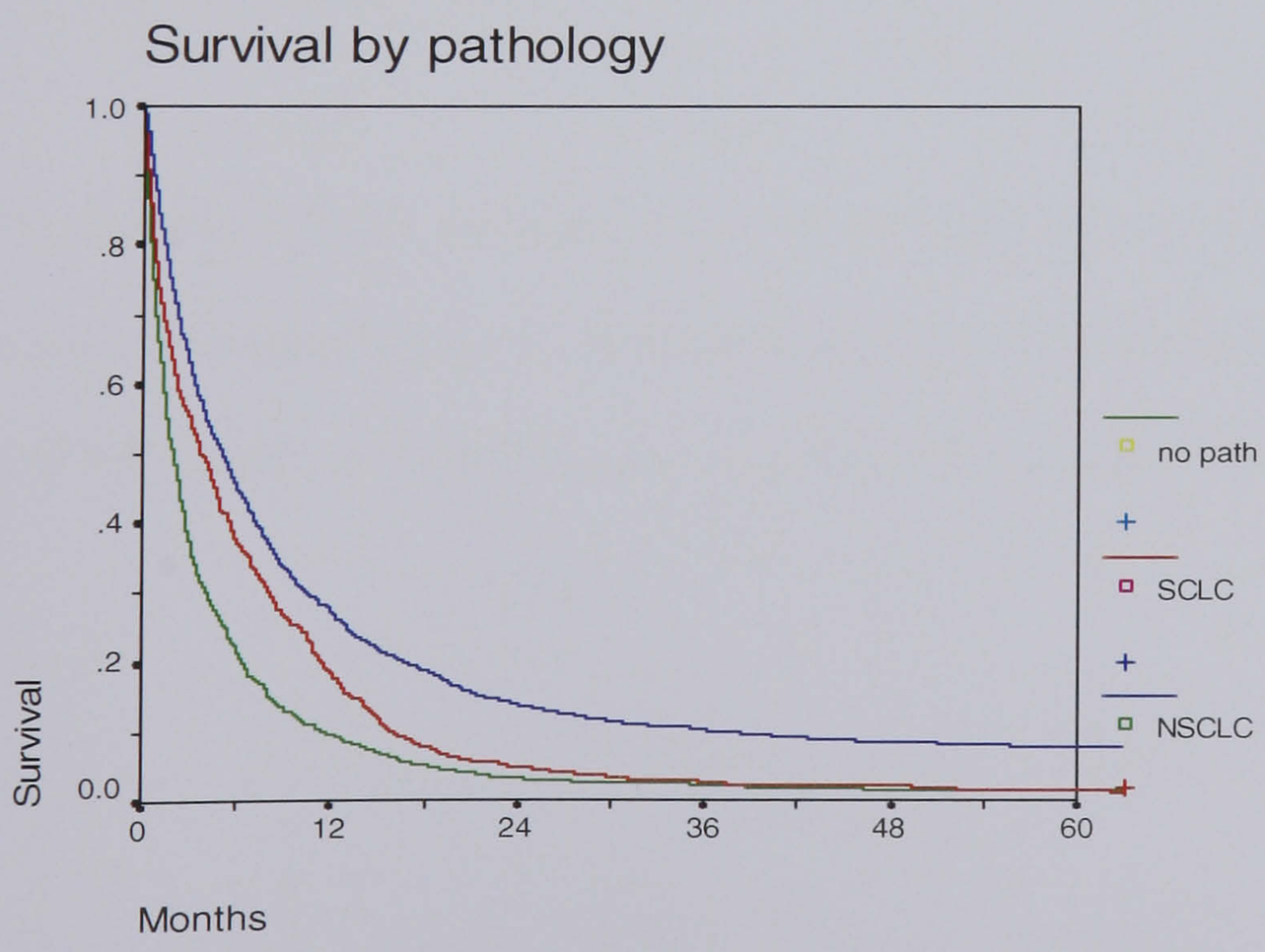
p<0.001

Figure 4.2c



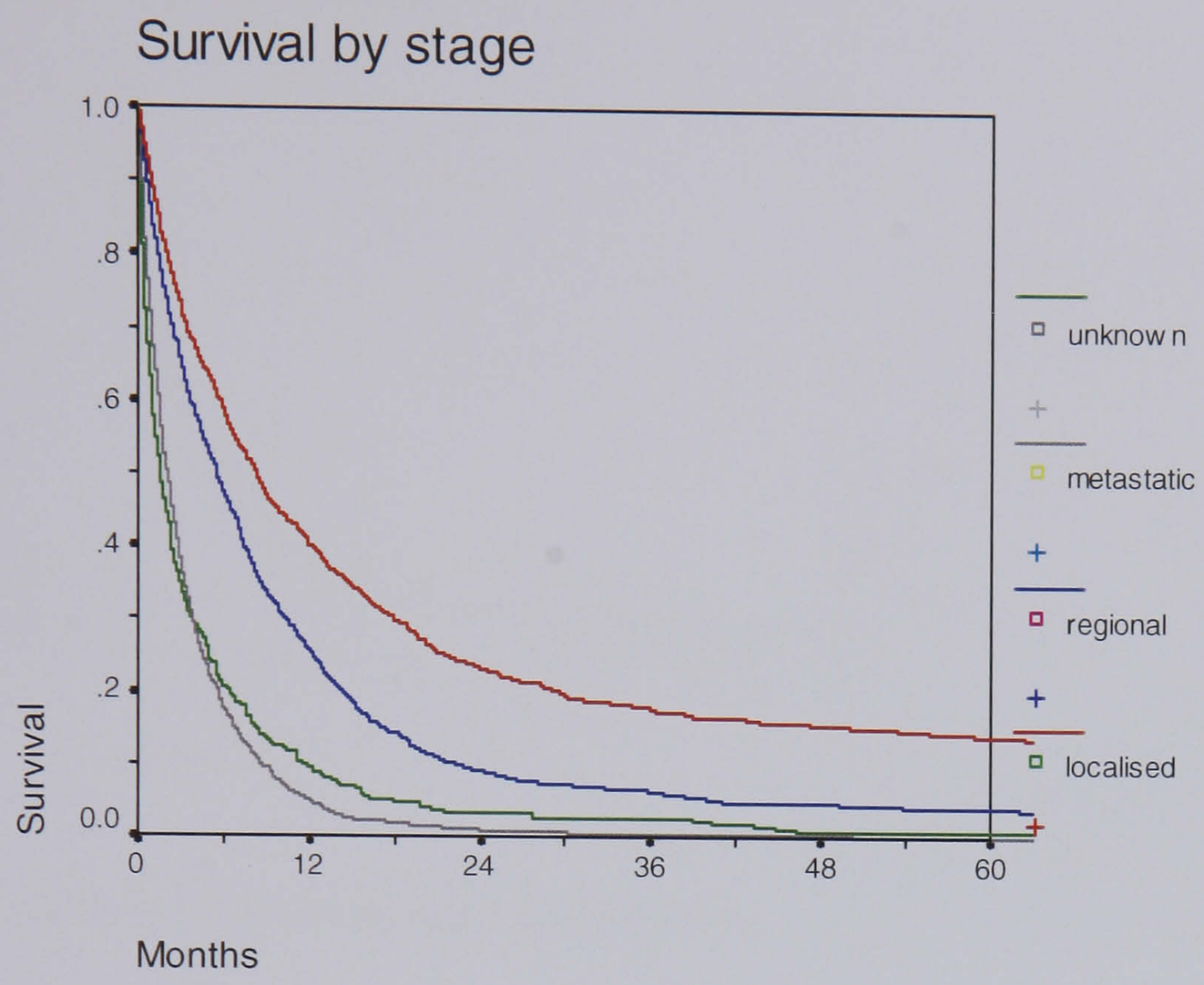
p=0.008

Figure 4.2d



p<0.001

Figure 4.2e

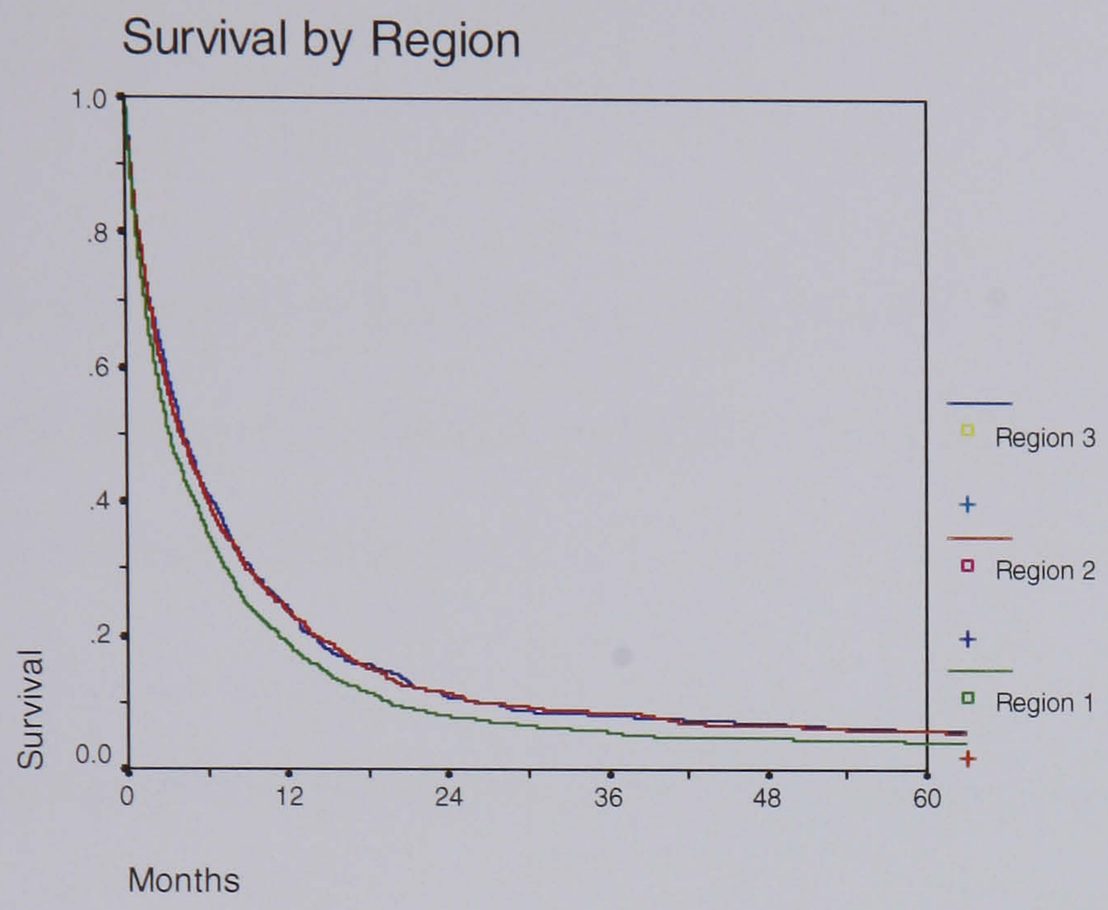


p<0.001

There was also a difference in survival between the three Regions (figure 4.2f); Region 1 median survival 3.2 months (2.9-3.5) Region 2, 4.1 months (3.5-4.6) and Region 3, 4.2month (3.7-4.8) (Log rank P<0.001).

If the variable 'Region' was then added to the Cox's regression model then journey distance was no longer significant, but there was a significant reduction in the risk of death in Region 2 (OR 0.87 (0.80-0.94)) and Region 3 (0.78 (0.71-0.86)) when compared with Region 1.

Figure 4.2f



$p<0.001$

7) Overall survival and treatment

A total of 548 patients in the cohort received potentially curative treatment and their median survival was 20.9 months (95% CI 18.3-23.5), with an overall survival rate of 69.2%, 46.5% and 29.5% at one, two and five years respectively. For the 1638 patients who received palliative treatment the median survival was 5.0 months (4.7-5.3), with 18.8% surviving one year and 4.4% two years. For the 1647 patients who received no treatment the median survival was 1.4 months (1.3-1.5), with a one year overall survival rate of 7.7%, and at two years 2.4%.

To further analyse the factors that could have had an impact on survival in each 'treatment intent' group, a Cox's regression model was conducted. The results are shown in Table 4.16.

The variable 'Region' was then added to each of the models. For those patients that received 'any treatment' there was a significant difference in the hazard ratio of death

between the regions (Region 2 0.86 (0.77-0.95) and Region 3 0.84 (0.75-0.94) compared with Region 1).

For the patients treated with 'potentially curative treatment', there was a significant reduction in the hazard ratio of death for Region 2 (0.71 (0.56-0.9) when compared with Region 1, but not for Region 3 (figure 4.3).

For the 'no treatment' group there was no difference between the Regions.

Figure 4.3

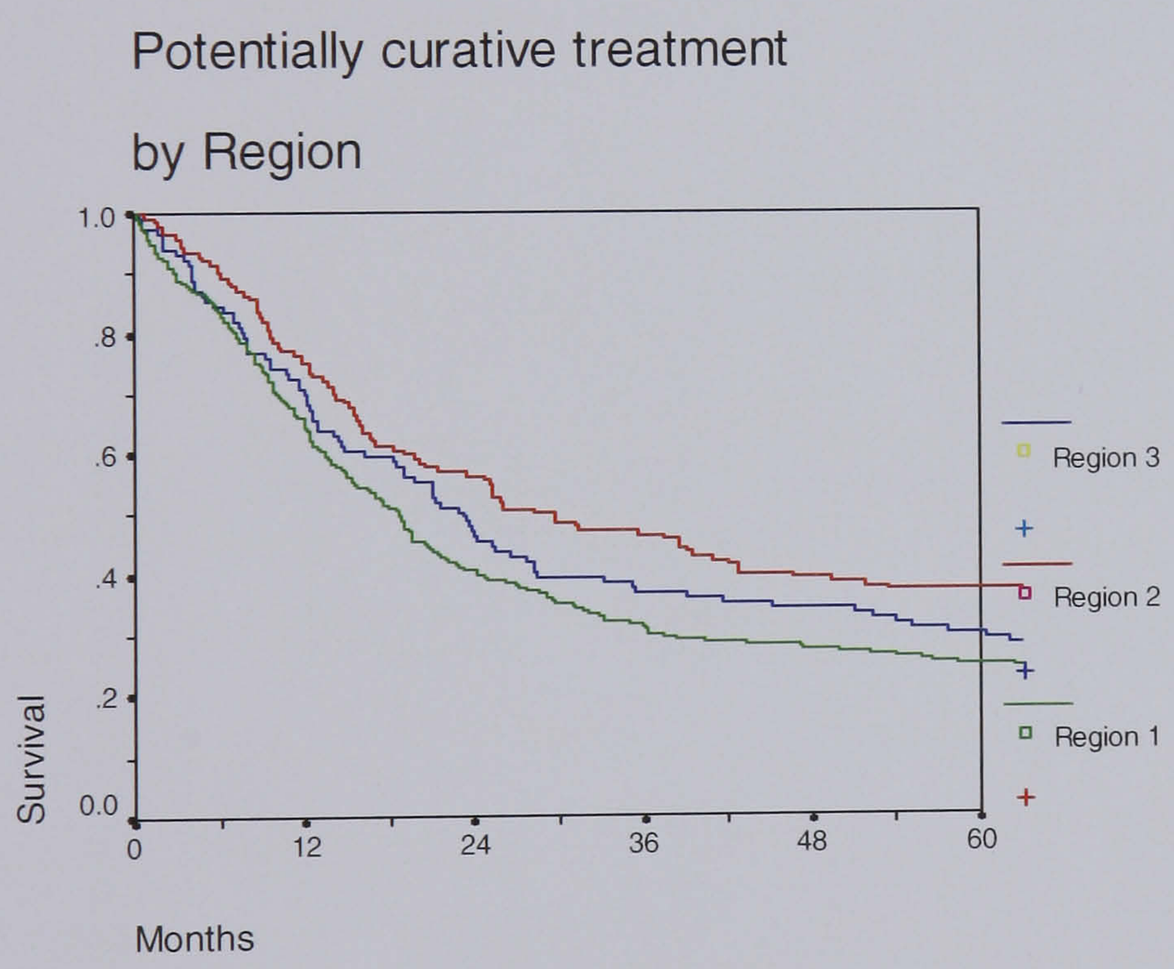


Table 4.16 – Overall survival and treatment intent

	ANY TREATMENT (N=2186)				POTENTIALLY CURATIVE (N=546)				NO TREATMENT (N=1647)			
	Median survival (months)	Log rank P value	Unadjusted hazard of death	Adjusted hazard of death	Median survival (months)	Log rank P value	Unadjusted hazard of death	Hazard ratio of death	Median survival (months)	Log rank P value	Unadjusted hazard of death	Hazard ratio of death
Male Female	6.5 (6.0-6.9) 6.8 (6.0-7.7)	0.22	1 0.9(0.86-1.03)	1 **0.9 (0.8-0.96)**	19.7 (16.3-21.1) 23.2 (18.2-28.2)	0.087	1 0.8(0.7-1.0)	1 0.8(0.7-1.0)	1.3 (1.1-1.4) 1.5 (1.3-1.7)	**0.039**	1 0.9(0.8-0.99)	1 **0.9 (0.8-0.98)**
<60 60-70 70-80 80+	7.6 (6.6-8.7) 7.4 (6.7-8.2) 5.9 (5.4-6.5) 4.0 (2.9-5.1)	**<0.001**	1 1.0(0.9-1.2) **1.3(1.2-1.5)** **1.9(1.5-2.3)**	1 1.1 (0.96-1.2) **1.5 (1.3-1.6)** **2.1(1.7-2.6)**	18.3 (12.8-2.9) 23.5 (18.7-26.4) 18.9 (14.3-23.5) 20.9 (7.2-34.7)	**0.025**	1 1.0(0.8-1.2) 1.2(1.0-1.2) 1.4(0.6-3.3)	1 1.0(0.8-1.3) **1.4(1.1-1.8)** 1.2(0.5-3.1)	1.6 (1.0-2.0) 1.4 (1.1-1.6) 1.5 (1.3-1.6) 1.3 (2.0-2.5)	0.08	1 1.1(0.9-1.4) 1.2(0.9-1.4) 1.3(1.0-1.6)	1 **1.4 (1.2-1.6)** **2.2 (1.9-2.6)** **1.8 (1.5-2.1)**
<1 hr >1hr	6.5 (6.1-7.0) 7.3 (5.6-9.0)	0.23	1 0.9(0.8-1.1)	1 1.0(0.8-1.1)	20.9 (18.2-23.7) 19.5 (13.1-25.9)	0.93	1 1.1(0.7-1.0)	1 1.3(0.8-1.6)	1.4 (1.2-1.5) 2.2 (1.0-3.3)	0.07	1 0.8(0.6-1.)	1 **0.8 (0.6-0.97)**
Cat 4-7 Cat 1-3	6.4 (5.9-6.9) 7.0 (6.1-7.8)	0.38	1 1.0(0.9-1.1)	1 0.9(0.8-1.0)	19.6 (16.7-22.5) 24.7 (19.8-29.6)	0.82	1 1.0(0.8-1.2)	1 1.0(0.8-1.2)	1.3 (1.2-1.5) 1.5 (1.3-1.7)	**0.02**	1 **0.9(0.8-0.98)**	1 **0.8 (0.7-0.9)**
NSCLC SCLC No path	7.6 (7.0-8.1) 5.6 (4.8-6.4) 4.4 (3.8-5.0)	**<0.001**	1 **1.6(1.4-1.7)** **1.8(1.6-2.0)**	1 **1.3(1.1-1.4)** **1.3(1.2-1.5)**	22.9 (19.4-26.4) 15.3 (13.8-14.8) 18.0 (10.1-27.8)	**0.002**	1 **1.6(1.2-2.1)** 1.6(0.9-2.7)	1 1.1(0.8-1.6) **1.8(1.02-3.0)**	1.7 (1.5-2.0) 0.6 (0.5-0.7) 1.3 (1.2-1.5)	**0.001**	1 **1.8(1.6-2.2)** **1.2(1.1-1.3)**	1 1.2(0.9-1.4) 1.1 (1.0-1.2)
Localised Regional Metastatic Unknown	11.9(10.7-13) 6.8 (6.2-7.4) 3.6 (3.3-4.0) 5.9 (4.3-7.4)	**<0.001**	1 **1.8(1.7-2.1)** **4.1(3.6-4.6)** **2.3(1.8-2.8)**	1 **1.8(1.6-2.0)** **3.6 (3.2-4.1)** **1.8 (1.4-2.2)**	23.3 (19.8-26.8) 16.1 (13.1-19.1) 12.9 (0-27.6) 27.6	**0.013**	1 **1.9(1.6-2.3)** **2.5(1.2-5.0)** 1.5(0.2-10.9)	1 **1.9(1.5-2.3)** **2.7(1.3-5.5)** 1.6(0.2-11.50	2.8 (2.3-3.4) 1.7 (1.5-2.0) 0.9 (0.8-1.0) 1.0 (0.8-1.2)	**0.001**	1 **1.4(1.2-1.6)** **2.2(1.9-2.6)** **1.8(1.6-2.1)**	1 **1.4 (1.2-1.6)** **2.2 (1.9-2.6)** **1.8 (1.5-2.1)**

1) Survival after potentially curative therapy

Resection

For the 406 patients who underwent a resection, the median survival was 26.2 months (21.2-31.2) with a one-year overall survival of 69.7%, two-year 52.9% and five-year 35.9%. The survival by detailed stage (when TNM available) and the alternative broader groups shown in Table 4.17 and figure 4.4.

Table 4.17 Overall survival following surgery by stage

	number	median	1 year	2 year	5 year
Stage I	163	64.6(45.9-83.4)	80.3%	70.5%	52.2%
Stage II	91	24.1 (17.5-30.6)	68.1%	51.9%	28.7%
Stage III	48	9.4 (7.0-11.7)	37.5%	12.5%	8.3%
Stage IV[1]	3	17.8 (9.9-25.7)	66%	33%	-
Unknown*	90	18.7 (12.3-25.1)	64.4%	43.3%	31.1%
Localised	244	45 (26.2-63.8)	75%	62%	45.9%
Regional	159	15.5	61%	39.6%	21.4%
Metastatic	3	17.8 (9.9-25.7)	66%	33%	-

*Remaining 11 limited stage SCLC

[1]Patients with solitary brain metastases or found to have a nodule in different lobe of lung at pneumonectomy

Figure 4.4 Overall survival following surgery according to pathological stage

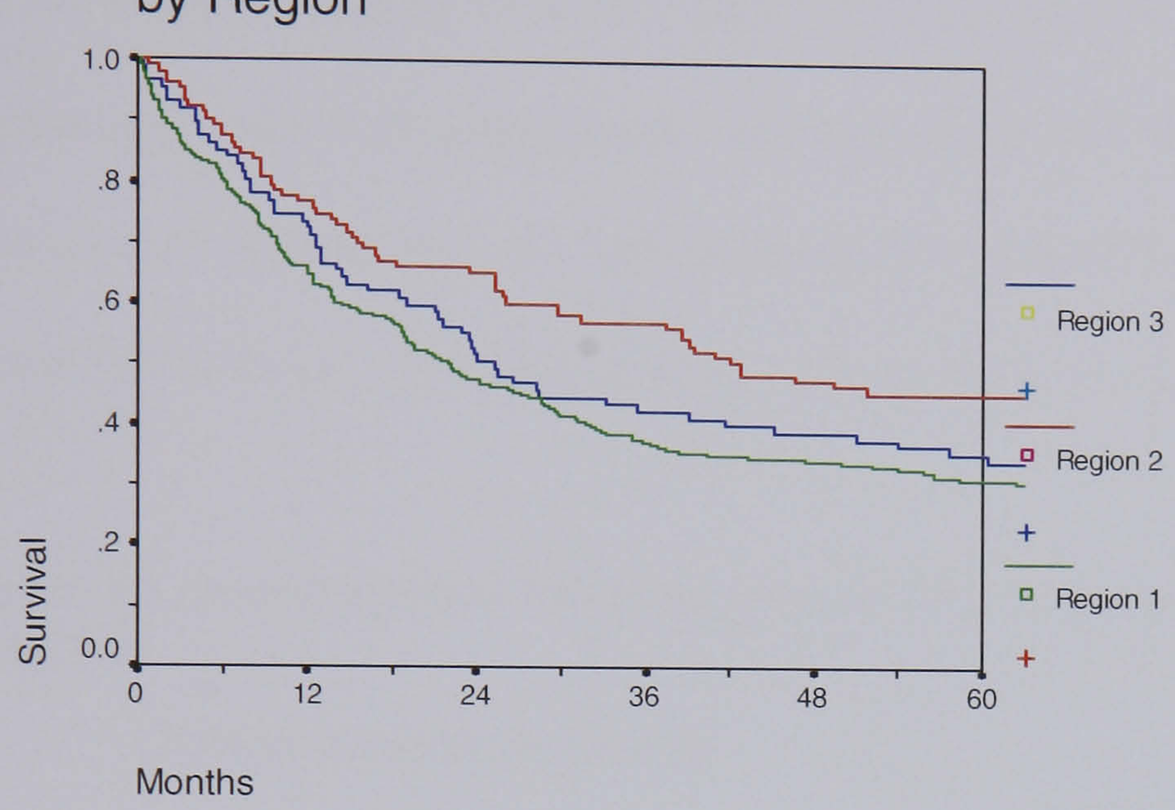
P<0.001

To investigate further the difference between the Regions in the survival of patients following potentially curative therapy (Figure 4.3), a log rank test was performed for the 406 patients who had undergone a resection and results are shown in Table 4.18 and figure 4.5. Patients from Region 2 who had their cancer resected had significantly longer survival (p=0.018) than the combined group from Region 1 and Region 3. In a Cox's regression model increasing age and stage were associated with an increased hazard of death, as was Region of diagnosis (Region 2 0.7 (0.5-0.9) and Region 3 0.8 (0.6-1.1) compared with Region 1).

Table 4.18 Overall survival of resected patients by Region

	Median survival (months)	1 month	1 year	5 year
Region 1 (n=216)	21.9 (16.4-27.5)	93.9%	65.3%	31.8%
Region 2 (n=103)	42.6 (19.4-65-9)	99.3%	66.0%	42.7%
Region 3 (n=87)	25.3 (19.8-30.7)	96.5%	72.4%	35.6%

Figure 4.5 Overall survival of resected cases by Region



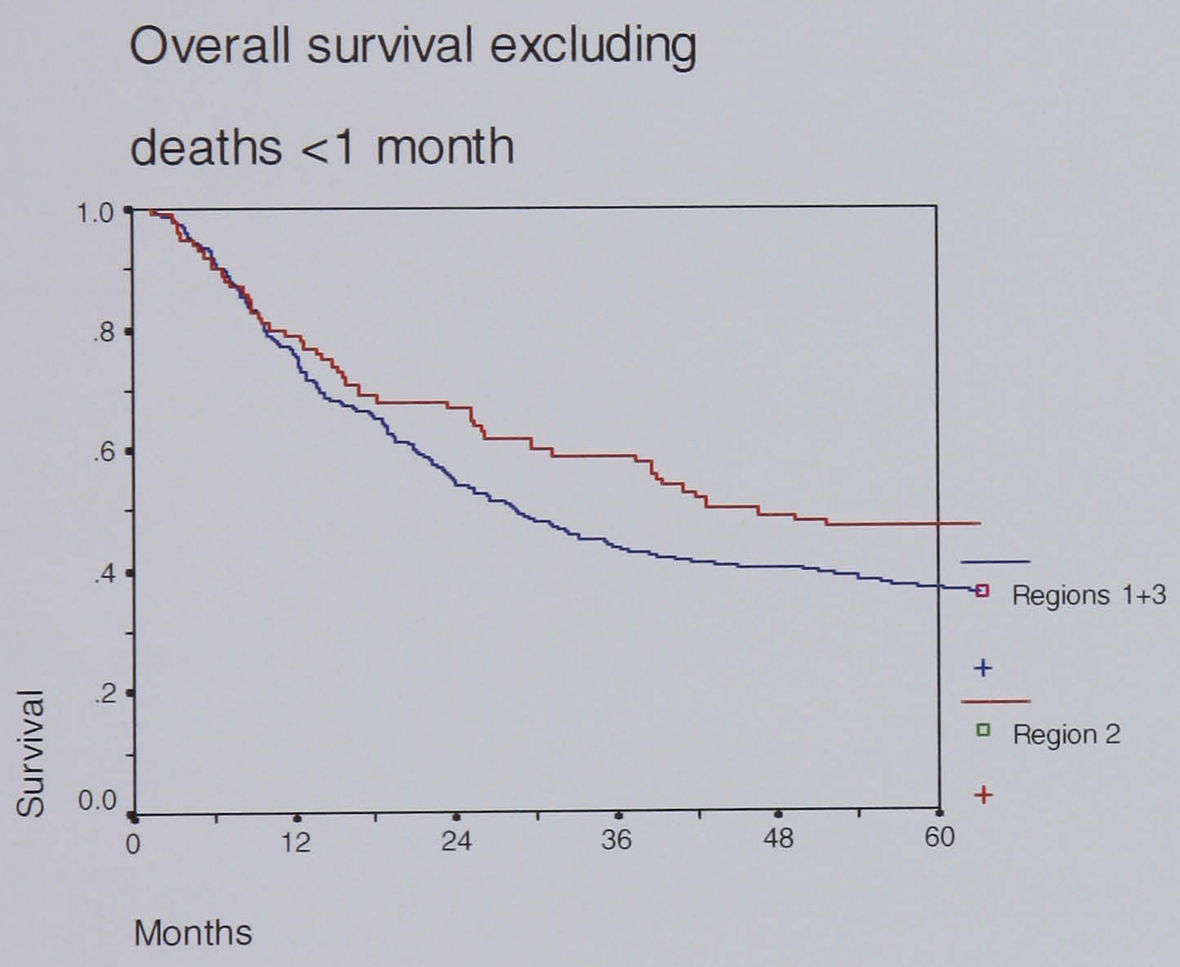
P=0.057

The post-operative mortality rate (37 post-resection and 3 post-thorocotomy) was 14.7% in Region 1 compared with 5.7% in Region 3 and 3% in Region 2 (Chi-squared p=0.02, Log rank comparing survival p=0.002) which could have had a major impact on the number of long term survivors. Though the difference in post-operative mortality might be partly explained by the fact there were fewer pneumonectomies performed in Region 2 (34%), compared with Region 1 (40%) and Region 3 (44%). The mortality following pneumonectomy in Region 2 at 6% was also lower when compared with 20% in Region 1, and 10% in Region 3.

When a multivariate analysis was performed examining the factors that could be associated with increased post-operative mortality (including age, gender, deprivation (as either dichotomous or categorical variable) and Region), only 'Region' and age over 70 years were associated with higher risk of death within one month of surgery.

If the 37 patients who died within a month of resection were excluded from the analysis then the survival was not statistically different between the Regions (median survival Region 2 42.7 (14.7-70.6) Region 1+3 28.5 (22.9-34.1) log rank P=0.11) (figure 4.6) and in a Cox's regression model only pathological stage was associated with an increased hazard of death. Therefore it appears that the high post-operative mortality was one of the most significant factors in the lower survival in patients undergoing potentially curative therapy in Region 1.

Figure 4.6 Overall survival following surgery after exclusion of patients dying with a month of surgery



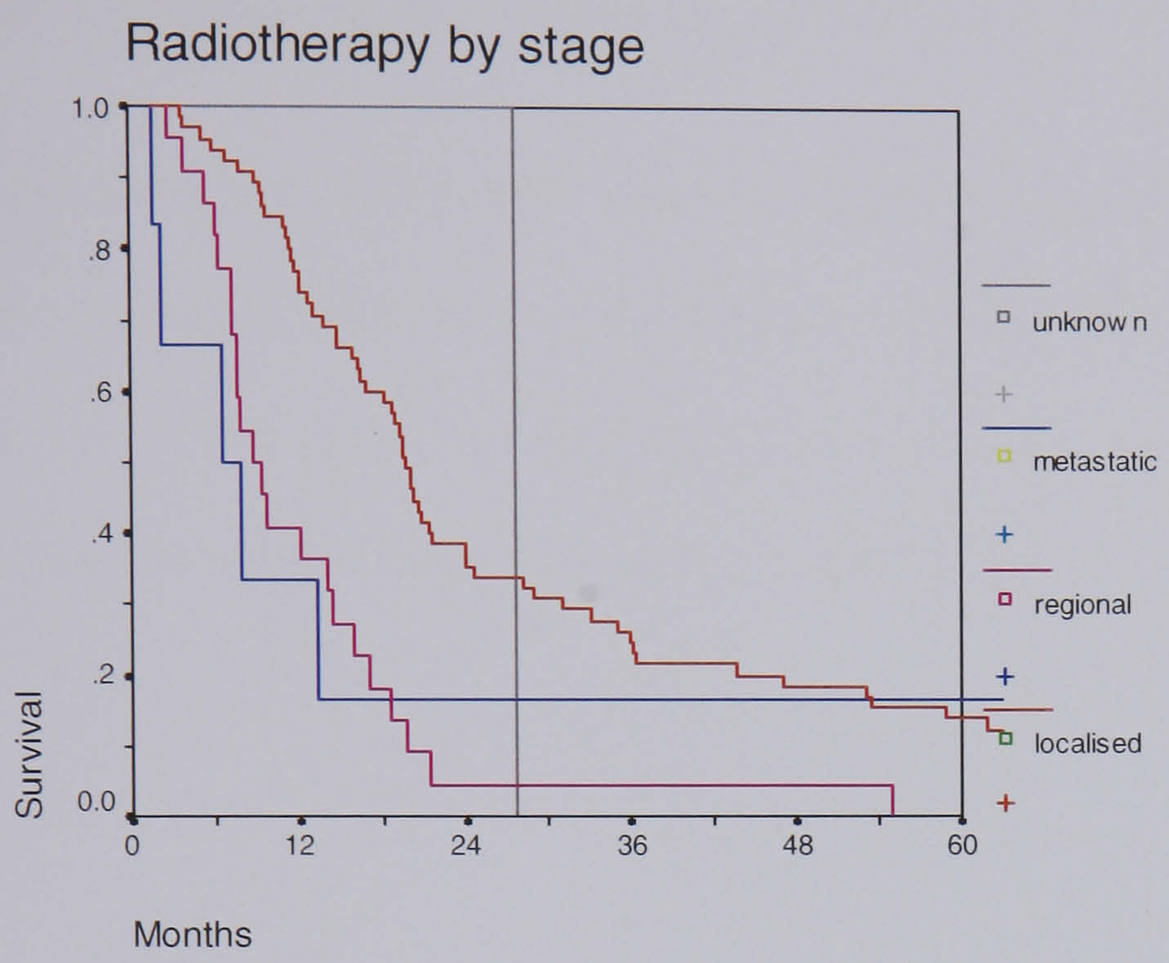
P=0.11

2) Radical Radiotherapy

There were 94 patients who received radical radiotherapy. This group had a median survival of 16.6 months (12.6-20.4) and an overall survival of 66% at one year, 29.8% two years and 10.6% five years (figure 4.6). If the survival by LRM stage was examined, the 65 patients with localised disease had a median survival of 19.7 months (18.1-21.3), the 22 with regional disease 8.8 months (6.4-11.02), and the six patients with metastatic disease 6.6 months (0.1-13.8). For the 59 cases with limited stage SCLC treated with curative intent, the median survival was 15.3 months (13.8-16.8) with a one-year overall survival rate of 67.8% and at five years 10.1%.

For those patients who received radical radiotherapy for NSCLC, only living in a less deprived area (median survival 28.2months (10.9-45.5) v 16.1months (12.7-19.39) log rank p=0.02) and presenting with localised disease (median survival 21.6months (16.8-26.4) v. regional 9.5months (6.7-12.2) log rank p<0.001) predicted for improved survival on uni-variate analysis. On Cox's regression analysis without the variable 'Region' the hazard for death was reduced for women (HR 0.46 (0.3-0.8), those living in more affluent areas (0.4 (0.2-0.7), and those with localised disease. These did not change when the variable 'Region' was added.

Figure 4.6



$p<0.001$

2) Survival by treatment modality

Table 4.19 shows the factors affecting survival for each of the three treatment modalities.

For patients with SCLC who received chemotherapy the median survival was 6.4months (5.6-7.2months), with 33% of the limited stage patients alive at one year, 8% at two-years and 3% at five years. For the NSCLC patients who received palliative chemotherapy the median survival was 7.0 months (5.4-8.8 months) and 24% were alive at one year.

Table 4.19 – Overall survival and treatment modality

	RESECTION* (N=406)				RADIOTHERAPY (N=1400)				CHEMOTHERAPY (N= 626)			
	Median Survival	Log rank P value	Unadjusted hazard of death	Adjusted hazard of death	Median Survival	Log rank P value	Unadjusted hazard of death	Adjusted hazard of death	Median Survival	Log rank P value	Unadjusted hazard of death	Adjusted hazard of death
Male Female	25.3 (19.7-30.8) 29.7 (17.2-42.2)	0.09	1 0.8(0.6-1.0)	1 0.9(0.8-1.1)	5.56 (5.1-6.0) 5.5 (4.7-6.2)	0.6	1 1.0(0.9-1.1)	1 0.9(0.8-1.04)	6.9 (5.9-7.8) 7.9 (6.6-9.1)	0.68	1 1.0(0.8-1.1)	1 **0.8(0.7-0.99)**
<60 60-69 70-79 80+	41.1 (8.6-39.1) 31.1 (20.6-41.6) 22.6 (16.1-29.1) 20.9 (0-52.1)	**0.028**	1 1.0(0.8-1.3) **1.5(1.1-2.0)** 1.9(0.6-6.1)	1 1.0 (0.8-1.3) **1.5 (1.1-2.0)** 1.9 (0.8-6.1)	6.0 (5.0-7.0) 5.9 (5.2-6.5) 5.5 (4.9-6.1) 4.0 (3.1-4.9)	**<0.001**	1 1.1(0.9-1.2) **1.2(1.03-1.4)** **1.5(1.2-1.9)**	1 1.1 (0.98-1.3) **1.4 (1.2-1.6)** **1.9 (1.5-2.4)**	8.4 (6.4-10.3) 8.1 (7.0-9.3) 5.4 (4.5-6.4) 6.4 (2.9-9.8)	**<0.001**	1 1.1(0.8-1.2) **1.5(1.2-1.9)** **1.7(1.1-2.9)**	1 1.1 (0.9-1.3) **1.4(1.2-1.8)** **2.1(1.3-3.3)**
<1 hr >1hr	25.8 (21.3-30.3) 31.6 ((0-68.7)	0.96	1 1.0(0.7-1.5)	1 1.1(0.7-1.6)	5.5 (5.1-5.9) 5.6 (4.2-7.0)	0.64	1 1.0(0.8-1.1)	1 0.9(0.8-1.1)	7.2 (6.4-8.0) 6.9 (2.3-11.6)	0.93	1 1.0(0.7-1.4)	1 1.1(0.8-1.6)
Cat 4-7 Cat 1-3	27.1 (20.4-32.9) 25.4 (20.8-30.4)	0.33	1 1.1(0.9-1.4)	1 1.1(0.9-1.5)	5.5 (5.1-5.9) 5.7 (4.8-6.5)	0.51	1 1.0(0.8-1.1)	1 0.9(0.8-1.0)	7.1 (6.2-8.0) 7.3 (5.9-8.7)	0.94	1 1.0(0.8-1.2)	1 1.0(0.8-1.2)
NSCLC SCLC No path	26.2 (21.2-31.3) 29.7 (10.3-49.1) -	0.99	1 1.0(0.5-2.0) -	1 0.7(0.3-1.3) -	5.8 (5.3-6.3) 6.8 (4.8-8.9) 4.3 (3.6-5.0)	**0.002**	1 1.0(0.8-1.2) **1.3(1.1-1.5)**	1 **0.8(0.7-0.98)** 1.1(1.0-1.3)	9.0 (8.1-10.4) 6.4 (5.6-7.2) 5.6 (0.7-10.5)	**<0.001**	1 **1.6(1.4-2.0)** **1.8(1.1-2.9)**	1 **1.2(1.0-1.5)** **1.1(0.7-1.9)**
Localised Regional Metastatic Unknown	26.5 (20-32.9) 23.1 (11.6-34.7) 17.8 (9.9-25.7) -	0.37	1 **1.9(1.5-2.4)** 2.3(0.8-7.5)	1 **1.9(1.5-2.4)** 2.6(0.8-8.1)	9.6 (8.4-10.8) 6.3 (5.6-7.0) 3.3 (2.9-3.6) 6.4 (4.3-8.5)	**<0.001**	1 **1.3(1.1-1.5)** **3.0(2.6-3.5)** **1.4-1.05-1.8)**	1 **1.5 (1.3-1.7)** **3.4 (2.9-3.9)** **1.4 (1.1-1.8)**	10.2 (8.911.6) 7.6 (6.3-9.0) 5.0 (4.1-5.9) 6.4 (3.6-9.0)	**<0.001**	1 **2.8(2.0-4.0)** **5.1(3.5-7.4)** **3.8(2.3-6.2)**	1 **2.391.6-3.4)** **4.6(3.1-6.9)** **2.9(1.7-4.9)**

Summary of results

- 4225 lung cancer cases were identified, of whom 3855 cases (91.2%) had sufficient data to conduct the audit.
- Of the 3855 cases 60.7% were male and the median age was 70.
- The pathological confirmation rate was 72%, with 20% adenocarcinoma, 39% squamous cancer, 24% small cell, 6% large cell and 11% other types of NSCLC.
- 25% of patients had localised disease, 33% regional, 31% metastatic, and in 11% the stage was unknown.
- Of the remaining 3833 patients, 14% were treated with curative intent, 43% received palliative treatment and 43% received no treatment.
- The resection rate was 11%.
- 37% of the population received radiotherapy during the first six months following diagnosis, but only 3% of the population received radical radiotherapy
- 16% of the population received chemotherapy, 63% of SCLC cases and 8% NSCLC
- Patients were more likely to receive treatment if they were younger, had loco-regional disease, had SCLC, or lived more than one hour's drive from a cancer centre. There were significant variations in the use of treatment between healthboards areas with an adjusted odds ratio of 3.0 for receiving any treatment for patients in North of Scotland compared with those living in the West of Scotland
- Younger patients, those with NSCLC, and those with localised disease were most likely to be treated with curative intent. There were also significant differences between the Regions with an adjusted odds ratio of 1.6 for patients from North of Scotland compared with those living in West of Scotland.

- Surgery was more commonly used in younger patients and those living in more affluent areas. There were no Regional variations in use of surgery.
- Radiotherapy was more likely to be given to younger patients, those with regional disease, NSCLC, and between the Regions. Patients from North of Scotland had an odds ratio of 2.8 for receiving radiotherapy compared with those from the West of Scotland.
- Chemotherapy was more likely to be delivered to younger patients and those with SCLC. There were no Regional differences in the use of chemotherapy.
- The median overall survival was 3.6 months with the survival rates of 21%, 9.5% and 4.9% at 1, 2 and 5 years, respectively.
- Younger age, being female, living in more affluent area and having the diagnosis pathologically confirmed were all associated with longer survival.
- There also appeared to be improved survival for those patients living in North and South-East of Scotland when compared with the West of Scotland.
- For patients undergoing a resection for their lung cancer the median survival was 26.2 months, with 36% alive at five years. Patient in the West and North of Scotland had lower odds of survival after surgery than those in South-East Scotland, but this appeared to be primarily due to a high rate of post-operative mortality, particularly in the West of Scotland
- Following radical radiotherapy for NSCLC the median survival was 16.6 months with 10.6% alive at five years, and following chemo-radiation for SCLC the figures were 15.3 months and 10.1%.

CHAPTER 5

Comparison of patient and tumour characteristics, treatment and survival for lung cancer in British Columbia and Scotland

Methods

The two datasets described in the previous two chapters were combined to enable comparison of patient and tumour related features, treatment and survival in Canada and Scotland. This file included 3833 Scots and 2073 Canadian patients. In order to make the populations as comparable as possible neither cohort contains any 'death-certificate-only' patients, and those who died the day they were diagnosed were also excluded.

Data on patient and tumour characteristics were compared using chi-square tests. Factors affecting treatment delivery were compared with chi-squared tests and logistic regression analyses, and survival using log rank tests and Cox's proportional hazards regression model. As discussed in the previous chapters any p-values between 0.05 and 0.01 should be treated with caution due to the number of analyses performed.

Results

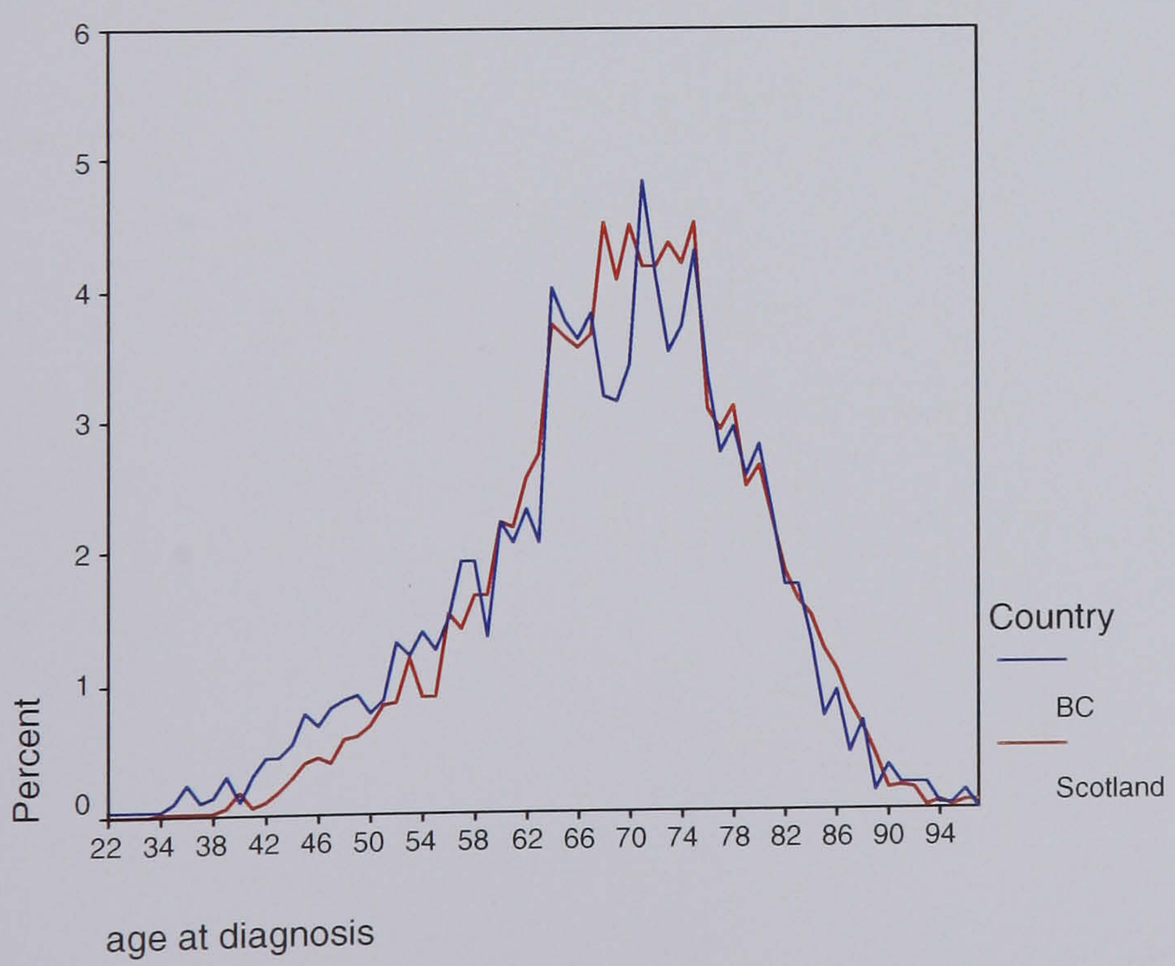
1) Characteristics

The patient characteristics are shown in Table 5.1. The patients diagnosed in BC were younger than those in Scotland, a result that remained statistically significant when age was examined as a continuous variable and compared using ANOVA ($p<0.001$). However, as demonstrated in figure 5.1, the differences are subtle.

Table 5.1Comparison of patient and tumour related factors in BC and Scotland

		BC	Scotland	Chi-squared
Gender	Male	1215 (58.6%)	2377 (60.7%)	P=0.12
	Female	858	1506	
Age	<60	424 (20.5%)	576 (15.0%)	**P<0.001**
	60-69	626 (30.2%)	1259 (32.8%)	
	70-79	735 (35.5%)	1437 (37.5%)	
	80+	288 (13.9%)	561 (14.6%)	
Travel	acceptable	1477 (71.3%)	3502 (93.2%)	**P<0.001**
	not acceptable	594	256	
	Least deprived	906 (43.7%)	1261 (39%)	**P<0.001**
	Most deprived	1165	2572	
Pathology	NSCLC	1540 (74.3%)	2168 (56.6%)	**P<0.001**
	SCLC	306 (14.8%)	674 (17.6%)	
	No pathology	227 (11.0%)	991 (26.9%)	
Stage	Localised	498 (24.0%)	964 (25.2%)	**P<0.001**
	Regional	538 (26.0%)	1254 (32.7%)	
	Metastatic	756 (36.5%)	1202 (31.4%)	
	Unknown	281 (13.6%)	694 (11.8%)	

Figure 5.1 Distribution of age in BC and Scotland cohorts



As one would expect with the geography of BC, more patients lived a significantly longer distance from a cancer centre in BC (28.3% >2 hours) than in Scotland (6.8% >1 hours).

Fewer patients underwent pathological confirmation in Scotland (74%) than in BC (89%). In Scotland 647 patients (18%) had SCLC compared with 306 (15%) in BC. There were also differences in the subtypes of NSCLC, with 51% of Scots having squamous cell carcinoma and 25% adenocarcinoma compared with 31% and 41% of British Columbians, respectively (χ^2 $p<0.001$).

In BC 74% of patients had a CT scan performed, but in Scotland only 48% had this procedure. Therefore it is probable that the apparently smaller proportion of patients with Stage IV disease in Scotland (31 v. 37%) was simply due to under-detection of metastases. However, as shown in Table 5.2 the differences in the stage for the patients who had had a CT scan was also significantly different (χ^2 $p<0.001$), but in both countries fewer patients with clinically obvious stage IV disease underwent a CT scan, so this cannot be the only explanation.

Table 5.2 Distribution of stage by CT scanning, country and pathological type

		BC no scan	Scotland no scan	BC with scan	Scotland with scan
NSCLC	Localised	70 (20%)	299 (34%)	375 (31%)	468 (37%)
	Regional	50 (15%)	178 (20%)	359 (30%)	516 (40%)
	Metastatic	138 (41%)	301 (34%)	316 (31%)	269 (21%)
	Unknown	83 (24%)	113 (13%)	94 (8%)	24 (2%)
SCLC	Limited	15 (20%)	212 (49%)	96 (41%)	139 (57%)
	Extensive	51 (70%)	188 (43%)	117 (50%)	98 (41%)
	Unknown	7 (10%)	33 (8%)	20 (9%)	4 (2%)
No pathology	Localised	30 (23%)	132 (20%)	23 (24%)	65 (20%)
	Regional	10 (7%)	95 (14%)	13 (14%)	114 (35%)
	Metastatic	45 (34%)	225 (34%)	29 (31%)	121 (37%)
	Unknown	48 (36%)	210 (32%)	29 (31%)	29 (9%)

2) Treatment

There was significantly greater use of treatment in BC than Scotland. Most importantly, more patients were treated with curative intent; 65% of British Columbians with early stage lung cancer received potentially curative therapy compared with 32% of Scots (χ^2<0.001) (see Table 5.3).

Table 5.3 Proportion of patients undergoing treatment in BC and Scotland

	BC	Scotland	Chi-squared
Treatment No treatment	1372 (66.2%) 701	2186 (57%) 1647	**P<0.001**
Potentially curative None/Palliative	546 (26.3%) 1527	548 (14.3%) 3285	**P<0.001**
Surgery No surgery	438 (21.1%) 1635	406(10.6%) 3227	**P<0.001**
Radiotherapy No radiotherapy	836 (40.3%) 1237	1400 (36.5%) 2433	**P=0.004**
Chemotherapy No chemotherapy	368 (17.8%) 1705	621 (16.2%) 3212	P=0.13

The use of the three treatment modalities in the two countries for each pathology group is shown in Tables 5.4a-c. The difference in the use of potentially curative treatment for NSCLC was due to a much higher proportion of patients undergoing resection. The radical radiotherapy rates were similar; 2.1% in BC and 2.5% Scotland.

Table 5.4a Proportion of use of treatment for NSCLC in BC and Scotland

NSCLC	BC	Scotland	Chi-squared
Surgery No surgery	425 (27.6%) 1115	395(18.2%) 1773	P<0.001
Radiotherapy No radiotherapy	649 (42.1%) 891	966 (44.6%) 1202	P=0.15
Chemotherapy No chemotherapy	133 (8.6%) 1407	178 (8.2%) 1990	P=0.67

Table 5.4b Proportion of use of treatment for SCLC in BC and Scotland

SCLC	BC	Scotland	Chi-squared
Surgery No surgery	8 (2.6%) 298	11 (1.6%) 663	P=0.32
Radiotherapy No radiotherapy	160 (52.3%) 160	180 (26.7%) 494	P<0.001
Chemotherapy No chemotherapy	231 (75.5%) 75	425 (63.1%) 249	P<0.001

Table 5.4c Proportion of use of treatment for 'no pathology' in BC and Scotland

No pathology	BC	Scotland	Chi-squared
Surgery No surgery	N/A	N/A	N/A
Radiotherapy No radiotherapy	27 (11.9%) 200	254 (25.6%) 737	P<0.001
Chemotherapy No chemotherapy	4 (1.8%) 223	18 (1.8%) 1196	P=1.0

To investigate if the differences in patient and tumour characteristics could explain the increased use of treatment in BC a multi-variate logistic regression analysis was performed (see Table 5.5). This demonstrated that even when differences in age, staging and pathology were taken into account, patients in BC were significantly more likely to receive 'any treatment' or 'potentially curative treatment'. The results changed little if just the CT staged patients were entered into the model.

Table 5.5 Multivariate analysis of factors affecting the use of 'any treatment' and potentially curative treatment'

	Unadjusted odds ratio of any treatment	Adjusted odds ratio of any treatment	Unadjusted odds ratio of PCT	Adjusted odds ratio of PCT
BC Scotland	1 **0.7(0.6-0.8)**	1 **0.7(0.62-0.82)**	1 0.47(0.41-0.53)	1 **0.4 (0.3-0.5)**
Male Female	1 1.0(0.8-1.1)	1 1.0(0.9-1.1)	1	1 1.0(0.9-1.2)
<60 60-69 70-79 80+	**1** **0.5 (0.4-0.6)** **0.28 (0.23-0.33)** **0.09 (0.07-0.11)**	1 **0.6(0.5-0.7)** **0.35(0.3-0.4)** **0.13(0.1-0.2)**	**1** **0.8(0.7-0.9)** **0.5(0.4-0.6)** **0.09(0.06-0.13)**	1 **0.7(0.6-0.9)** **0.4(0.3-0.5)** **0.08(0.05-0.13)**
Travel acceptable not acceptable	1 **1.3(1.1-1.5)**	1 1.1(1.0-1.4)	1 1.6(1.4-1.9)	1 1.2(0.9-1.5)
Most deprived Least deprived	1 **1.3 (1.1-1.4)**	1 **1.3 (1.2-1.5)**	1 **1.3(1.1-1.5)**	1 **1.3 (1.1-1.5)**
NSCLC SCLC No pathology	1 **1.6 (0.4-1.9)** **0.16 (0.1-0.2)**	1 **2.0 (1.6-2.3)** **0.3 (0.2-0.3)**	1 0.5(0.4-0.6) **0.06 (0.03-0.08)**	1 1.0 (0.8-1.3) **0.1 (0.1-0.2)**
Localised Regional Metastatic Unknown	1 **1.2(0.05-1.4)** **0.6 (0.5-0.7)** **0.12(0.1-0.16)**	1 0.9 (0.8-1.1) **0.4 (0.4-0.5)** **0.1 (0.1-0.2)**	1 0.45(0.4-0.5) **0.01 (0.0-0.02)** **0.0 (80-0.1)**	1 **0.35 (0.3-0.4)** **0.0** **0.08 (0.06-0.13)**

When individual treatment modalities were examined in a logistic regression model the use of surgery and chemotherapy was significantly higher in BC than Scotland, but the use of radiotherapy was similar (see Table 5.6).

Table 5.6 Factors affecting the use of the different treatment modalities

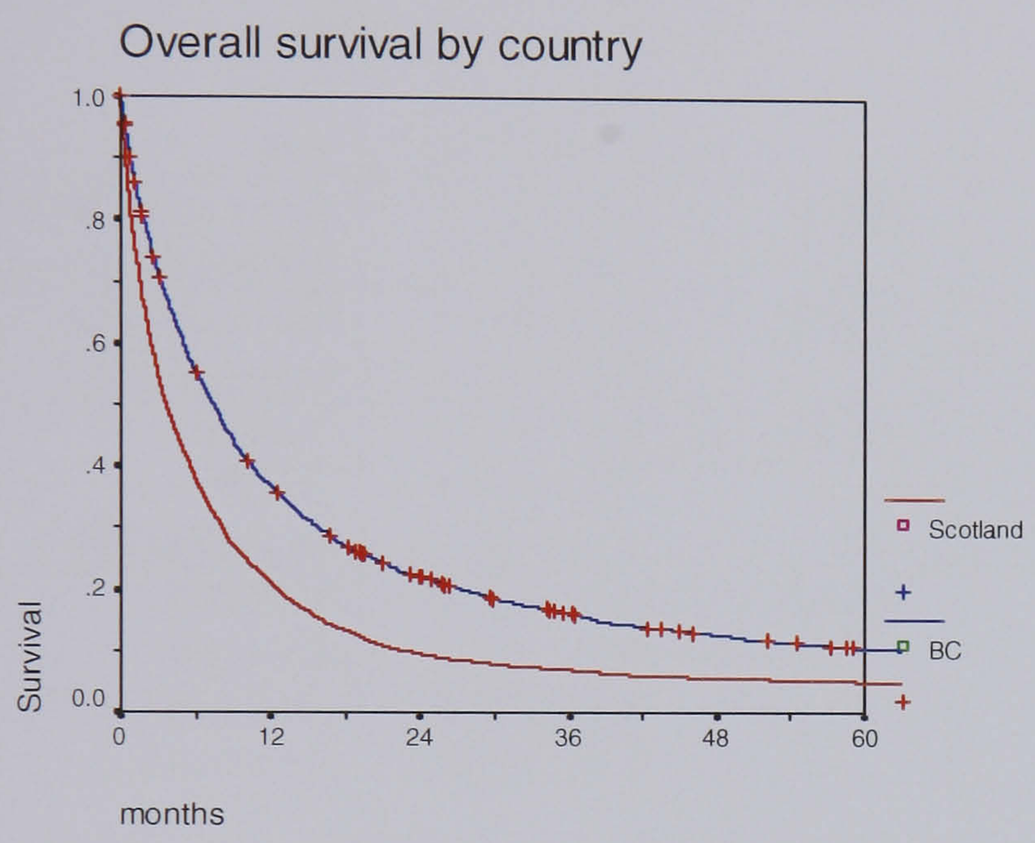
Gender and travel times were also entered into the model but neither affected the odds of use of any treatment modality

		RESECTION		RADIOTHERAPY		CHEMOTHERAPY	
		Unadjusted odds ratio	Adjusted odds ratio	Unadjusted odds ratio	Adjusted odds ratio	Unadjusted odds ratio	Adjusted odds ratio
Country	BC	1	1	1	1	1	1
	Scotland	**0.42(0.37-0.49)**	**0.36 (0.3-0.44)**	**0.85(0.76-0.95)**	0.9(0.8-1.04)	0.9(0.8-1.03)	**0.8 (0.6-0.9)**
	Male	1	1	1	1	1	1
	Female	1.0(0.9-1.2)	1.1(0.9-1.3)	**0.9(0.8-0.97)**	0.9(0.8-1.1)	**1.2(1.02-1.3)**	0.9(0.8-1.2)
Age	<60	**1**	**1**	**1**	**1**	**1**	1
	60-69	**0.8(0.7-0.97)**	**0.7(0.6-0.9)**	**0.7(0.6-0.8)**	**0.8(0.7-0.9)**	**0.6(0.4-0.7)**	**0.4(0.3-0.5)**
	70-79	**0.5(0.4-0.6)**	**0.4(0.3-0.5)**	**0.6(0.5-0.7)**	**0.7(0.6-0.9)**	**0.3(0.2-0.4)**	**0.2(0.1-0.3)**
	80+	**0.08(0.05-0.12)**	**0.07(0.04-0.12)**	**0.3(0.2-0.4)**	**0.5(0.4-0.6)**	**0.09(0.06-0.14)**	**0.07(0.04-0.1)**
	Travel acceptable	1	1	1	1	1	1
	not acceptable	**1.7(1.4-2.0)**	1.1(0.9-1.4)	1.1(0.9-1.2)	1.0(0.8-1.1)	0.9(0.8-1.1)	0.8(0.6-1.1)
	Most deprived	1	1	1	1	1	1
	Least deprived	**1.3(1.1-1.5)**	**1.3 (1.1-1.5)**	**1.2(1.05-1.3)**	**1.2 (1.03-1.3)**	1.1(0.99-1.3)	**1.3 (1.04-1.5)**
Pathology	NSCLC	1	1	1	1	1	1
	SCLC	**0.08(0.05-0.12)**	**0.1 (0.1-0.2)**	**0.7(0.6-0.8)**	**0.5 (0.5-0.6)**	**22.1(18.5-26.4)**	**26.1 (21.0-32.3)**
	No pathology	**0.02(0-0.03)**	**0.03 (0.0-0.07)**	**0.4(0.3-0.5)**	**0.5 (0.4-0.6)**	**0.2(0.1-0.3)**	**0.4 (0.2-0.6)**
Stage	Localised	1	1	1	1	1	1
	Regional	**0.35(0.3-0.4)**	**0.4 (0.3-0.5)**	**1.7(0.5-2.0)**	**1.9 (1.7-2.3)**	**6.9(5.3-9.0)**	**2.1 (1.5-2.8)**
	Metastatic	**0.03(0.02-0.04)**	**0.2 (0.0-0.3)**	**1.4(1.2-1.6)**	**1.7 (1.4-1.9)**	**5.5(4.2-7.2)**	**1.6 (1.2-2.1)**
	Unknown	**0.1(0.02-0.14)**	**0.14(0.1-0.19)**	**0.2(0.16-0.3)**	**0.3 (0.2-0.4)**	**1.8(1.2-2.5)**	1.2 (0.7-1.8)

3) Survival

The median survival for the Scottish patients was 3.6months (3.4-3.9), and in BC 7.3months (6.8-8.0) (log rank p<0.001 figure 5.2).

Figure 5.2 Overall survival



p<0.001

As previously demonstrated in the analyses of the individual counties, shorter survival was observed for older patients, male patients, those living in more deprived areas or closer to a cancer centre, patients with no pathology, or with more advanced-stage disease (log rank P</= 0.001 for all, see Table 5.7).

In the Cox's regression model these factors, except distance to cancer centre, remained statistically significant (p values </=0.001 see Table 5.7). The hazard of death for lung cancer patients living in Scotland in 1995 was 1.6 times that of the BC patients even when variations in patient characteristics, tumour type and stage were accounted for.

Table 5.7 Univariate and multivariate analysis of factors affecting survival

N= 5906	Median (months)	Log rank P value	Unadjusted hazard ratio of death	Adjusted hazard ratio of death
BC	7.4 (6.8-8.0)	**<0.001**	1	1
Scotland	3.6 (3.4-3.9)		**1.5(1.4-1.6)**	**1.6 (1.5-1.7)**
Male	4.6 (4.3-5.0)	**0.001**	1	1
Female	4.9 (4.5-5.3)		**0.91(0.86-0.96)**	**0.9 (0.8-0.9)**
<60	7.6 (6.8-8.4)	**<0.001**	1	1
60-69	5.9 (5.4-6.4)		**1.15(1.1-1.2)**	**1.2 (1.1-1.3)**
70-79	4.0 (3.6-4.4)		**1.5(1.4-1.6)**	**1.5 (1.4-1.7)**
80+	2.2 (1.9-2.5)		**2.1(1.9-2.3)**	**2.0(1.8-2.2)**
Travel acceptable	4.4 (4.1-4.6)	**<0.001**	1	1
not acceptable	7.1 (6.3-8.0)		**0.77(0.71-0.83)**	0.9 (0.8-1.0)
Most deprived	4.4 (4.0-4.6)	**<0.001**	1	1
Least deprived	5.4 (4.9-5.9)		**0.89(0.84-0.94)**	**0.9 (0.86-0.96)**
NSCLC	6.2 (5.8-6.5)	**<0.001**	1	1
SCLC	4.8 (4.2-5.3)		**1.4(1.3-1.5)**	1.1(0.98-1.2)
No pathology	2.1(1.8-2.3)		**2.1(2.0-2.3)**	**1.5 (1.4-1.6)**
Localised	11.8 (10.6-13.1)	**<0.001**	1	1
Regional	6.9(6.5-7.4)		**1.6(1.5-1.7)**	**1.7 (1.6-1.8)**
Metastatic	2.5(2.4-2.7)		**3.3(3.0-3.6)**	**3.7 (3.4-4.0)**
Unknown	2.0(1.7-2.3)		**2.8(2.6-3.1)**	**2.5 (2.3-2.8)**

To ensure that difference in the proportion of CT-staged patients between the two countries had no impact, the Cox's regression model was then repeated including just the 1847 Scots and 1526 Canadians who had been CT-staged. Even for this completely staged group of patients, the hazard ratio of death was increased in Scotland (1.4 (1.3-15) P<0.001), as it was for all the other variables, except travel times.

If the model was repeated for just the CT staged patients with NSCLC (n=2476) there were no differences in the adjusted hazard of death between the pathological subtypes (adenocarcinoma, squamous cell, large cell v NSCLC NOS) but the adjusted hazard of death for Scotland was 1.37(1.2-1.5).

Cause specific survival

A total of 1869 (90.2%) of the British Columbian patients died within five years of diagnosis, 1667 (89%) of lung cancer and 202 (11%) of other causes, whereas 3370 (96%) of the Scottish patients died, 3067 (91%) of lung cancer.

The hazard of death from lung cancer within five years of diagnosis was 1.6 times greater in Scotland than in BC (Table 5.11)

Table 5.11 Cox's* regression *model of cause specific survival

N= 5906	Unadjusted hazard ratio of lung cancer death	Adjusted hazard ratio of lung cancer death
BC	1	1
Scotland	**1.55(1.45-1.64)**	**1.62 (1.52-1.73)**
Male	1	1
Female	**0.93(0.88-0.98)**	**0.90 (0.85-0.96)**
<60	1	1
60-69	**1.1(1.02-1.2)**	**1.13 (1.04-1.23)**
70-79	**1.4(1.3-1.6)**	**1.49 (1.37-1.62)**
80+	**2.0(1.8-2.2)**	**1.98 (1.78-2.20)**
acceptable	1	1
not acceptable	**0.75(0.69-0.81)**	**0.89 (0.82-0.97)**
Most deprived	1	1
Least deprived	**0.88(0.83-0.93)**	**0.90 (0.85-0.95)**
NSCLC	1	1
SCLC	**1.5(1.5-1.6)**	1.04 (0.96-1.12)
No pathology	**2.1(1.9-2.2)**	**1.44 (1.33-1.55)**
Localised	1	1
Regional	**1.7(1.6-1.9)**	**1.82 (1.68-1.98)**
Metastatic	**3.6(3.3-3.9)**	**4.05 (3.73-4.41)**
Unknown	**2.8(2.5-3.1)**	**2.53 (2.27-2.82)**

Relative Survival

One of the potential explanations for a variation in survival observed between two countries is different profiles of disease. Cox's proportional hazard regression analysis adjusts for different age profiles within populations, but does not account for age-specific differences in all cause mortality between countries. For example in 1995, a sixty-five year old male in BC had a life expectancy of 16.9 years compared with 13.8 years for a Scottish man of the same age.

In order to adjust for this the relative survival, which calculates the excess mortality in a group of patients compared with the whole population, was calculated using the technique described by Dickman et al[52][1]. The life-Tables for British Columbia and Scotland covering the period of the study were obtained and used to calculate the expected survival of each group taking into account the gender and age distribution within each cohort. The survival in the two populations was then compared.

The one, two and five-year survival figures are shown in Table 5.8a and figure 5.3. It can be seen that patients with lung cancer in Scotland had a markedly inferior survival even when differences in general all cause mortality in BC and Scotland were taken into account.

Table 5.8b shows the five-year survival broken down by age and gender. The survival rates were superior in BC for all groups except women over the age of 80.

[1]Performed by Dr Linda Williams, Medical Statistics Unit, University of Edinburgh

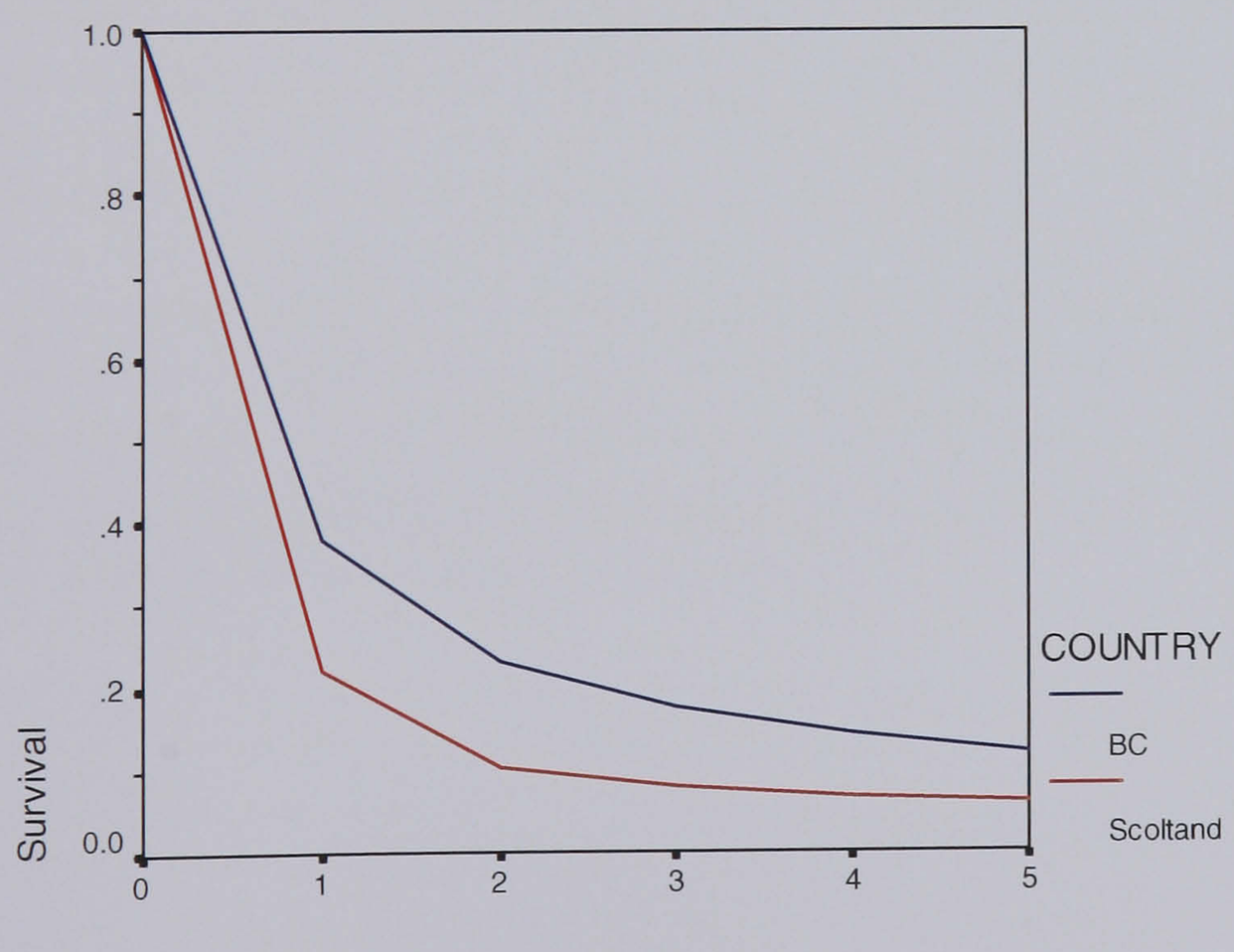
Table 5.8a Relative survival rates for Scotland and BC

	1-year	2- year	five-year
Scotland (n=3833)	22% (21-24%)	10% (9-11%)	6% (5-7%)
British Columbia (n=2070)	38% (36-40%)	23% (21-25%)	12% (10-14%)

Table 5.8b Five-year relative survival rates by gender and age group

Five-year relative survival		Scotland	BC
Male	<60	10.2%	13.3%
	60-69	7.6%	11.6%
	70-79	4.0%	8.5%
	80+	0.7%	6.6%
Female	<60	8.6%	16.9%
	60-69	9.4%	20.1%
	70-79	3.0%	11.3%
	80+	3.1%	2.4%

Figure 5.3 *Relative survival for BC v Scotland*



p<0.001

To explore the data further, a relative survival model was estimated using four different methods as described by Dickman et al[52]. They differ in the manner in which the data are entered and the assumptions about the data used. The results are shown in Table 5.9.

Table 5.9 Risks of death using the four models described by Dickman et al.

	Grouped		Exact times	
	Binary	Poisson	Individual data	Collapsed times
Deviance	88.7	72.1		116.7
Residual df	70	70		70
Estimated excess hazard ratios (p-value)				
Follow up 1/5[1]	9.58 (<0.0001)	8.64 (<0.0001)	10.52 (<0.0001)	10.58 (<0.0001)
Follow up 2/5	4.99 (<0.0001)	4.96 (<0.0001)	5.11 (<0.0001)	5.14 (<0.0001)
Follow up 3/5	2.33 (<0.0001)	2.38 (<0.0001)	2.35 (<0.0001)	2.37 (<0.0001)
Follow up 4/5	1.66 (0.0089)	1.68 (0.0093)	1.68 (0.0068)	1.70 (0.0060)
Female/Male	0.93 (0.0220)	0.96 (0.1344)	0.93 (0.0304)	0.93 (0.0150)
60-69/<60[2]	1.03 (0.4479)	1.02 (0.6580)	1.09 (0.0447)	1.09 (0.0441)
70-79/<60	1.31 (<0.0001)	1.20 (<0.0001)	1.44 (<0.0001)	1.45 (<0.0001)
80+/<60	1.72 (<0.0001)	1.34 (<0.0001)	2.11 (<0.0001)	2.12 (<0.0001)
BC/Scotland	0.67 (<0.0001)	0.74 (<0.0001)	0.62 (<0.0001)	0.62 (<0.0001)

[1]Ratio of risk of death in first to fifth year following diagnosis
[2]Ratio of risk of death compared to patients aged <60

These models demonstrated: -

a) The excess risk of death was much greater in the first two years following diagnosis.

b) The main excess risk was observed in the oldest group of patients; those over 80 had an excess lung cancer mortality was around twice that of the youngest group of patients.

c) When the increased life expectancy of women in the general population was taken into account women still had a reduced hazard of death compared with men.

d) When differences in overall life-expectancy were taken into account, the hazard of mortality in BC was about two-thirds that of the Scottish patients.

4) Possible explanations for the inferior overall survival in Scotland

The question is therefore, was the inferior survival of the Scottish patients simply due to under-use of treatment? In order to take account for the lower use of treatment an additional variable, 'treatment intent' (none, potentially curative, palliative), was added to the Cox's regression model examining factors influencing hazard of death from all causes (overall survival). This had no impact (hazard ratio death Scotland v BC (1.5 (1.4-1.6)). The difference in the hazard ratio of death between the two countries also remained significant when only the CT staged patients were included in the model.

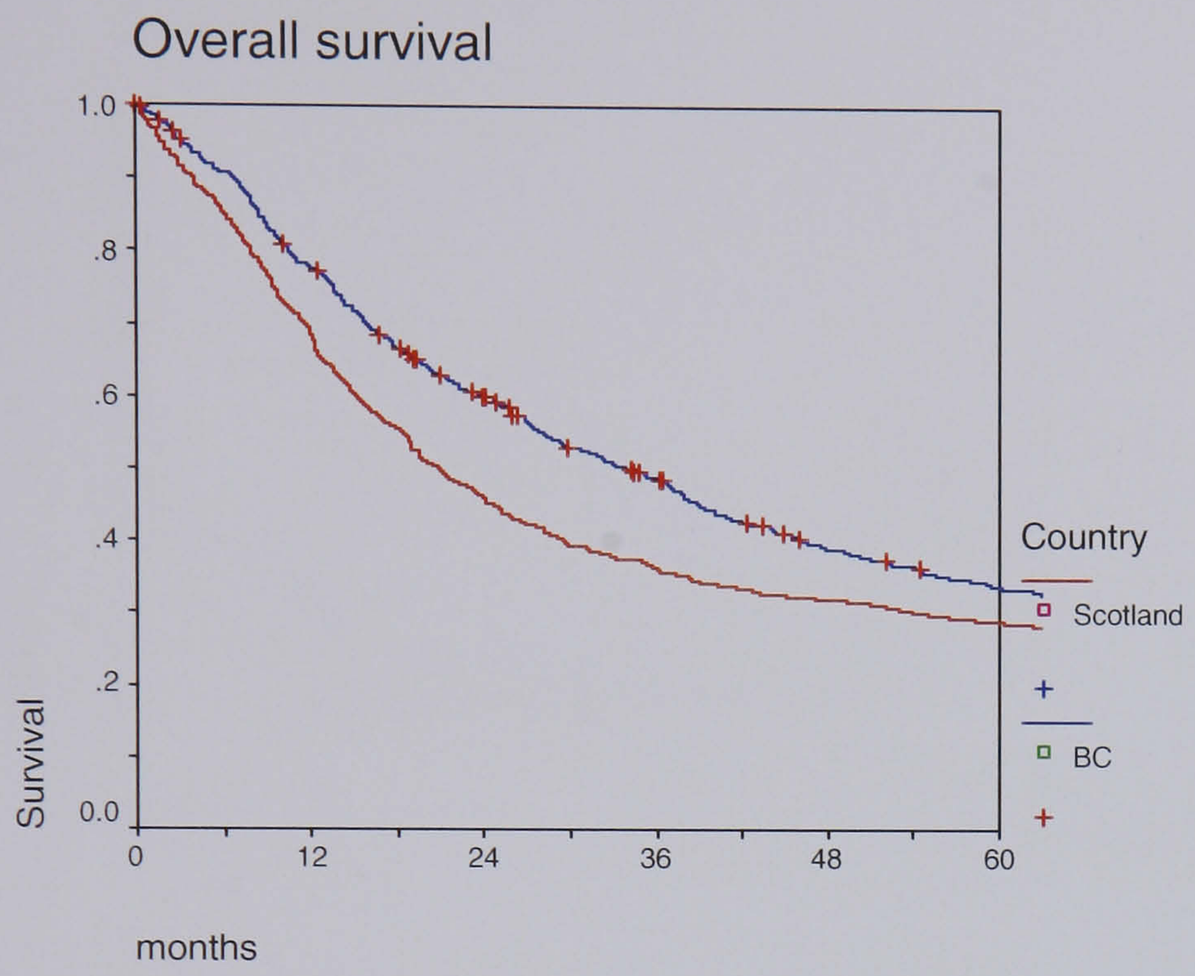
The survival for patients in Scotland was significantly worse on univariate and multivariate analyses regardless of treatment intent; potentially curative therapy hazard ratio death 1.3 (1.13-1.51) (figure 5.4a log rank p=0.001), palliative treatment hazard ratio death 1.42 (1.3-1.56) (figure 5.4b p<0.001), and no treatment hazard ratio of death was 1.48 (1.34-1.64) (figure 5.4c p<0.001). The median, one, two and five year survival rates are shown in Table 5.12.

Table 5.12 Survival rates in BC and Scotland by treatment intent

		Median (months)	1 year	2 year	5 year
Potentially curative Therapy	BC	34.0 (29.4-38.5)	77%	60%	34%
	Scotland	20.9 (18.3-23.5)	68%	46%	29%
Palliative treatment	BC	6.3 (5.8-6.8)	23%	8%	2%
	Scotland	5.0 (4.7-5.3)	19%	4%	1%
No treatment	BC	2.5 (2.1-2.8)	21%	9%	2%
	Scotland	1.4 (1.3-1.5)	8%	2%	0.1%

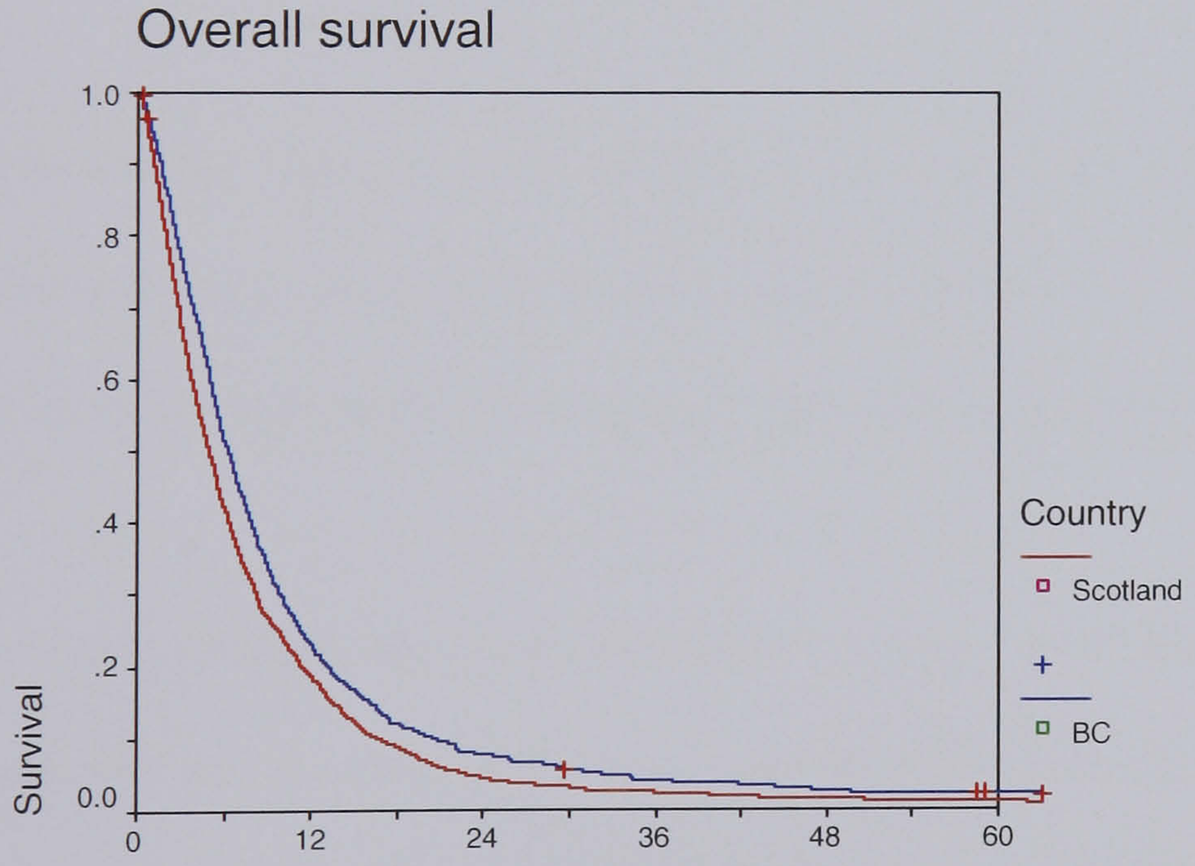
The treatment modality used had no impact; patients in Scotland had an increased hazard of death for all treatment types (surgery HR death 1.3 (1.1-1.6), radiotherapy 1.5 (1.4-1.6), chemotherapy 1.5 (1.3-1.8)).

Figure 5.4a (potentially curative treatment)



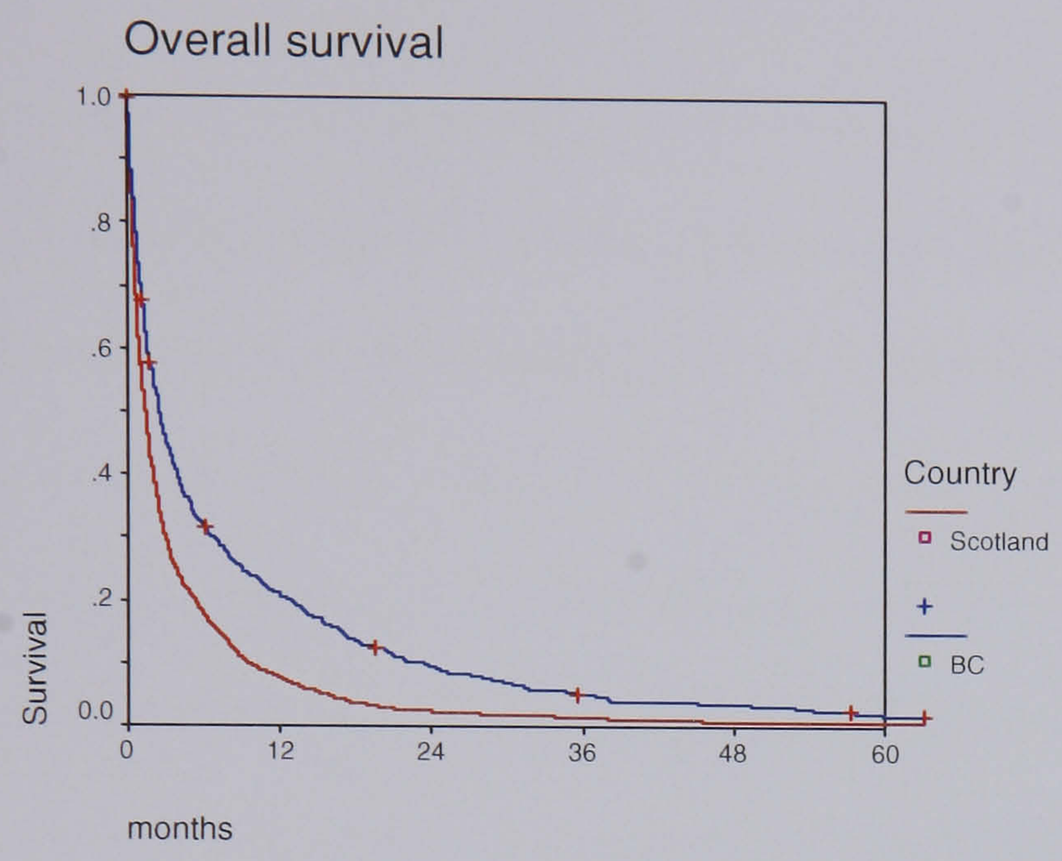
p=0.001

Figure 5.4b -palliative treatment



p<0.001

Figure 5.4c No treatment



p<0.001

So if it was not just the increased use of treatment in BC that accounted for the superior survival were there any other patient or tumour related factors that could have contributed?

Unfortunately data on some important factors, which are known to predict for overall survival in lung cancer, such as performance status and co-morbid diseases [190, 205], were not recorded with sufficient frequency and accuracy to be used in this analysis.

However, patients who undergo surgery for lung cancer generally have a better performance status and less co-morbidity so by examining the survival for this group the variability of these factors should be minimised. Therefore, further logistic regression and Cox's regression analyses were performed including just the 844 patients who had had surgery for their lung cancer (Table 5.13).

Comparison of surgical patients

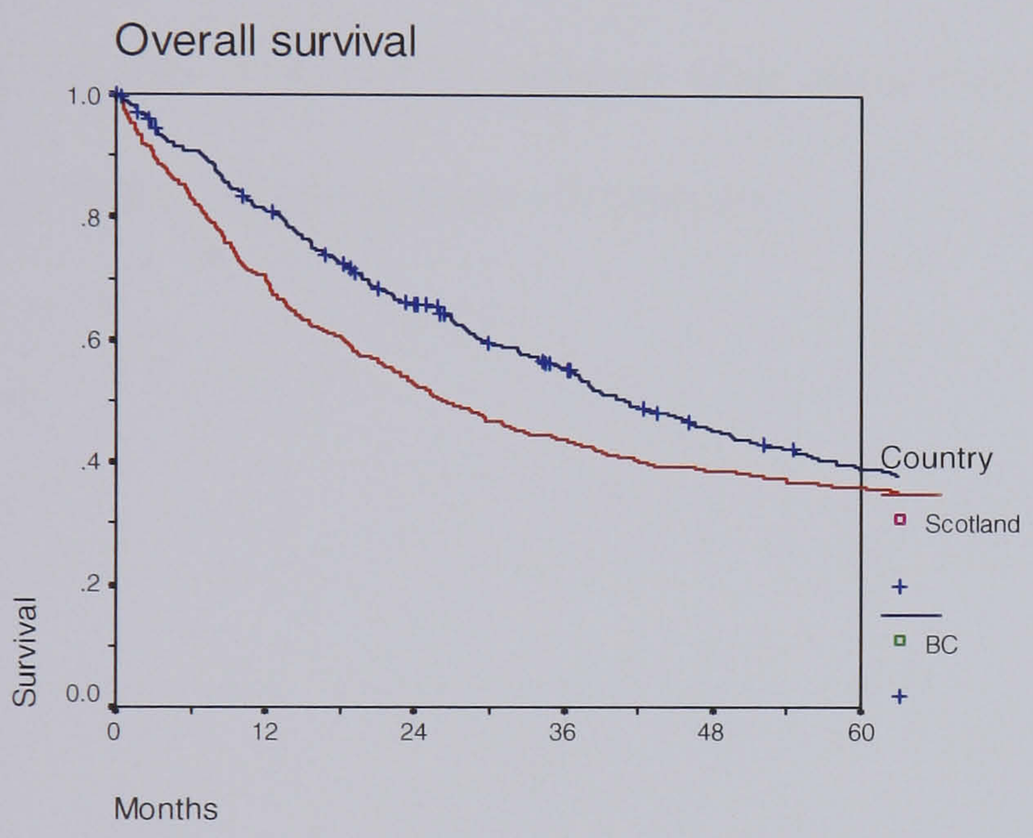
In order to ensure as accurate as possible staging a more detailed staging system was used for this analysis. Of the 844 surgical cases, detailed staging (pathological TNM) was available for 719 patients. For the remaining 129 cases, the 84 labelled as having 'localised disease' were reclassified as 'Stage I', and the 9 with 'regional' disease as Stage III, leaving just 36 (4%) with unknown staging. In the Scottish audit the definition of localised and regional disease depended on nodal status, so a T4N0M0 tumour may have been recorded as localised, but in the process above would be inadvertently called this Stage I rather than Stage III.

Table 5.13 – Univariate and multivariate analysis of survival of the patients under going a resection

N=844	Median (months)	Log rank P value	Unadjusted hazard of death	Adjusted hazard ratio of death
BC	40.9 (35.1-46.6)	**0.018**	1	1
Scotland	20.1 (20.0-28.5)		**1.2(1.04-1.4)**	**1.3 (1.1-1.6)**
Male	30.1 (25.2-35.1))	**0.003**	**1**	1
Female	41.9 (32.1-51.9)		**0.8(0.7-0.9)**	0.9(0.7-1.02)
<60	39.3 (27.3-51.5)	**0.002**	**1**	1
60-69	38.2 (28.2-48.1)		**1.0(0.8-1.3)**	1.1 (0.8-1.4)
70-79	31.6 (25.5-37.7))		**1.4(1.2-1.8)**	**1.5 (1.2-2.0)**
80+	27.3 (14.5-40.0)		**1.4(0.8-2.5)**	1.7 (0.9-3.1)
Travel acceptable	32.4 (27.8-37.0)	0.50	1	1
not acceptable	41.3 (30.9-51.6)		0.9(0.8-1.1)	1.0(0.8-1.3)
Most deprived	36.7 (30.8-42.5)	0.46	1	1
Least deprived	32.2 (25.2-39.2)		1.1(0.9-1.3)	1.1(0.9-1.3)
NSCLC	35.5 (30.8-40.2)	0.24	1	1
SCLC	29.7 (6.4-52.9)		1.0(0.6-1.7)	1.3(0.7-2.2)
No pathology	22.2 (0-55.5)		2.1(0.9-5.0)	2.1(0.9-5.3)
I	53.2 (42-62.0)	**0.001**	1	1
II	24.0 (17.4-30.6)		**1.7(1.4-2.1)**	**1.7(1.4-2.1)**
III	14.1 (9.1-19.1)		**2.5(2.0-3.2)**	**2.7(2.1-3.3)**
IV	13.7 (4.6-22.8)		**2.8(1.6-4.9)**	**2.9(1.6-5.1)**
Limit	29.7 (6.4-53.0)		1.3(0.7-2.2)	-
Unknown	44.1(22.6-65.5)		1.3(0.8-1.9)	1.3(0.9-1.3)

Even for this sub-group of 844 patients, the hazard ratio of death was 1.3 (1.1-1.6) for Scotland compared with BC. The median survival in BC was 41months, whereas in Scotland it was 26months (see figure5.5 and Table 5.10, log rank P=0.018) The 1-year, 2-year and five-year survival was 81%, 66%, 39% (CI 44-34%) in BC, and 70%, 53%, 36% (95% CI 41-31%) in Scotland, respectively.

Figure 5.5 Resected only cases



p=0.018

However, as the rate of post-operative death was much higher in Scotland than BC and could have been a contributory factor to the inferior early survival in Scotland. Therefore the analyses were repeated after having removed the 49 patients who died within a month of surgery. For the remaining 795 surgical patients the difference in the survival in a univariate analysis was no longer statistically significant (median survival 42months BC v 32months Scotland, log rank p= 0.19, HR death 1.1(0.9-1.2)), but the multivariate analysis demonstrated that patients in Scotland still had an increased hazard of death (HR 1.23(1.02-1.49)).

Tumour pathology

In some surgical series, patients with adenocarcinoma have been noted to have improved survival compared with other pathological subtypes. In BC 205 (47%) of the resected tumours were adenocarcinomas compared with 138 (34%) in Scotland. If the outcome following a resection for the patients with adenocarcinoma was compared with the 333 with squamous cell tumours in a Cox' regression model then the hazard ratio of death was not significantly different for patients with adenocarcinoma (HR 1.1(0.9-1.3)) when compared with those with squamous cell tumours.

Summary of results

- The patients in Scotland were slightly older.
- Around 40% of cases occurred in women in both countries.
- More cases in Scotland did not have pathological confirmation (26% v 11%). There appeared to be more patients with adenocarcinomas in BC, but this could be artefact from fewer patients in Scotland having a pathological diagnosis.
- The proportion of patients with local stage disease was similar, but there were more patients with regional disease in Scotland (33% v 26% BC) and more patients with metastatic disease in BC (31% v 37% BC). However, this may be due to greater use of CT staging in Canada (74% CT in BC v 48% Scotland).
- Even when differences of age, stage or pathology were taken into account the adjusted odds of a patient receiving any sort of treatment in Scotland was 0.7 compared with BC and 0.4 for under going potentially curative treatment.
- The resection rate for patients with NSCLC was 28 % in BC and 18% in Scotland
- The median survival was twice as long in BC as Scotland
- The differences in survival could not be accounted for by differences in patient age, gender, tumour stage, or tumour type.
- The relative survival at one, two and five years were 38%, 24%, 12 % in BC and 22%, 10%, 6% in Scotland, respectively.
- For all treatment intent groups (potentially curative, palliative and no treatment) and treatment modalities (surgery, radiotherapy or chemotherapy) patients in Scotland had inferior survival.
- The shorter survival following surgery could not be completely explained by the higher post-operative mortality in Scotland or difference in pathological subtypes.

CHAPTER 6

Have treatment and survival improved in South-East Scotland since 1995?

Introduction

Since the 1995 audit was conducted there have been a number of changes to healthcare organisation and the staff treating lung cancer in South-East Scotland.

These changes have included:

1. The introduction of managed clinical networks (South-East Scotland Cancer Network or SCAN) to ensure smoother referral pathways and better patient management.
2. The introduction of national patient management guidelines through the Scottish Intercollegiate Guidelines Network (SIGN). The first lung cancer guidelines were published in 1998 and revised in 2005.
3. The introduction of multi-disciplinary team meetings in all the main hospitals, at which all newly diagnosed patients are discussed.
4. Appointment of more oncologists specialising in lung cancer; the number increased from two in 1995 to four in 2002 (a fifth (SCE) was appointed third-quarter 2002). So, all patients should have the opportunity to benefit from the opinion of a specialist respiratory oncologist.

Other changes in clinical practice have also occurred, primarily:

1. Greater access to CT scanning and the development of scanners with improved image quality
2. Increasing evidence supporting the use of palliative chemotherapy in NSCLC
3. Increasing evidence on the use of chemo-radiation in limited stage SCLC

4. More experience with 3D-conformal radiotherapy, so patients with large tumours or poor pulmonary function who would have been previous declined are now offered this treatment.

Therefore, the question is have these changes resulted in an improvement in treatment and survival of lung cancer patients in South-East Scotland?

The aims of this study were therefore to compare a new cohort from 2002 with the original 1995 cohort to assess

1. The proportion of lung cancer patients receiving treatment
2. The median, one and two-year survival of lung cancer patients

Methods

SCAN covers a population of 1.25 million in the four Scottish healthboard regions of Lothian, Borders, Fife, and Dumfries & Galloway. All radiotherapy is delivered at the Edinburgh Cancer Centre (ECC), which in 2002 had five linear accelerators. The majority of chemotherapy is delivered under the supervision of an oncologist, but in 2002 respiratory physicians in the Royal Infirmary of Edinburgh, Borders General Hospital, Victoria Hospital Fife, and Dumfries and Galloway Royal Infirmary administered some chemotherapy.

Lung cancer surgery is performed in the Royal Infirmary in Edinburgh, but patients living in Dumfries and Galloway usually have their surgery performed in Glasgow. Therefore, for this study *only* patients living in Lothian, Borders and Fife were included.

Integral to the development of the cancer networks has been the introduction of prospective audit to monitor patient characteristics and management. The audit was commenced in 2001, and by 2002 systems were in place to identify most of the patients diagnosed with lung cancer in the SCAN region. Cases are identified through the multi-disciplinary team meetings, pathology reports, the ECC database, and Scottish Cancer Registry reports.

Data on patient characteristics including date of birth, gender, address, and performance status are collected. Tumour details are recorded, including how the diagnosis was made, staging investigations performed, pathological type and stage. Staging is recorded where possible according to the TNM staging, but some cases only have stage recorded as local (confined to lung), regional (involvement of hilar or mediastinal lymph nodes) or metastatic.

Since 1995, the allocation of deprivation indices across Scotland has altered and it is recommended that the Carstairs index based on the 2001 census be used [98]. Therefore, each patient post-code was linked to the 2001 Carstairs Index.

Since 1974, the Edinburgh Cancer Centre (ECC) has had a computerised database that includes data on all referred patients and includes details of all radiotherapy and chemotherapy treatments delivered under the supervision of the oncologists and tracks patients' survival until death.

Firstly, patients diagnosed with lung cancer in 2002 that resided in Lothian, Borders and Fife healthboard areas were identified from the SCAN and the ECC databases. Then pharmacy records from all the hospitals were cross-checked with the database to ensure all chemotherapy episodes had been identified. The hard-copy records of all thoracic operations were hand-searched and details of all lung cancer resections recorded.

Once a final list of patients who had received treatment under the care of the SCAN lung cancer team had been prepared, the database was then given to the Scottish Cancer Registry to identify any missing cases. Details on the patients who had not been identified by the audit, but had died were supplied to the research staff to check the medical records. For the patients who were not identified by the audit and who were still alive, only name, date of birth and contact details of their general practitioner (GP) were supplied. A condition of the ethical approval for this study was that these patients were required to give consent before the release of more detailed information.

The medical records of the additional cases were then scrutinized to assess if they were eligible for entry into the audit and patient, tumour and management details recorded. For those patients whose notes could not be identified additional letters were sent to their general practitioners to ask for further details (see Appendix 2).

The details of all cancer therapies delivered within six months of diagnosis were recorded. An exception was made for consolidation radiotherapy after chemotherapy in limited stage SCLC as this is part of the 'initial treatment package', but can commence during the seventh month.

Treatment intent was defined as for the 1995 audit, with potentially curative therapy defined as either surgery, radical radiotherapy with a dose of 50Gy or more, or chemo-radiation with thoracic radiotherapy with a dose of 30Gy or more for limited stage small-cell lung cancer (L-SCLC)

In order to obtain up-to-date survival, the records of the General Register Office of Scotland were searched for notification of any patient deaths.

Once the database for 2002 patients was finalised comparison was then made with the 1995 audit patients from Lothian, Borders and Fife.

The Multi-Centre Ethics Research Committee for Scotland granted ethical approval for this study.

Analysis

Patient, tumour and management characteristics were analysed using descriptive statistics and compared using either chi-squared for categorical or ANOVA for continuous variables. Factors affecting the probability of use of treatment were examined using logistic regression models. Due to the different lengths of follow-up between the 1995 and 2002 cohorts, survival was censored at two years and estimated using the Kaplan Meier method and compared using log-rank tests and Cox's regression model.

Results

A total of 877 patients living in the three health board areas were first diagnosed with lung cancer during 2002 and had been identified by the SCAN audit. The Scottish Cancer Registry identified a possible additional 347 cases. However, of these 32 were first diagnosed in another year (1999-2003), 156 were already on the 2002 database, but with slightly different spellings of name or date of birth, 5 had a different primary (mesothelioma, prostate cancer or carcinoma of unknown primary) and were felt by an oncologist (SCE) not to definitely have lung cancer, and 4 lived outside the healthboard areas. Therefore, an additional 107 cases were confirmed by either the hospital or general practitioner (GP) medical records and were added to the database. For 43 cases neither the hospital nor GP medical records could be located (unverified cases).

Only *two* patients with possible lung cancer were still alive, but had not been under the care of a SCAN lung cancer physician. One was known to have dementia and the second had moved outside the region so neither patient could be contacted for permission to access their records. These cases were therefore excluded.

Therefore a total 984 confirmed cases and 43 unconfirmed cases were identified.

1) Patient characteristics

The patient characteristics are shown in Table 6.1. There were no significant differences in the characteristics of the verified and unverified patents. The diagnosis was confirmed with pathology in 716 (73%) of the verified cases, 8 were confirmed at post-mortem and 260 were diagnosed on radiology alone. In 86 (33%) of the radiological only diagnosis cases biopsies were performed, but were negative.

For the 43 cases in whom the medical records could not be located, according to the registry data, 11 (26%) were histologically confirmed; 5 adenocarcinoma, 2 squamous cell and 4 non-small cell not otherwise specified (NSCLC NOS).

Table 6.1 Patient and tumour characteristics of all the patients diagnosed in 2002

		Verified Cases	Unverified	Whole cohort
	Number	984	43	1027
Gender	Male	543 (55%)	24 (56%)	
Age	Median	72.5	77.8	73.0
	Range	37-94	65-93	37-94
Carstairs	1	152 (15%)	4 (9%)	156 (15%)
	2	178 (18%)	9 (21%)	187 (18%)
	3	222 (23%)	11 (26%)	233 (23%)
	4	318 (32%)	14 (33%)	332 (32%)
	5	114 (12%)	5 (12%)	119 (12%)
Healthboard	Lothian	611 (62%)	27(63%)	638 (62%)
	Borders	92 (9%)	4 (9%)	96 (9%)
	Fife	281 (29%)	12 (28%)	293 (29%)
Performance Status	0-1	396 (41%)		
	2	221 (22%)	Not known	-
	3-4	235 (24%)		
	Not known	132 (13%)		

χ^2 - No significant differences between verified and unverified cases

The variations in the patient characteristics between patients from the health board areas and these are shown in Table 6.2. Patients from Fife live in more deprived areas than those in Lothian or Borders.

Table 6.2 Patient and tumour characteristics in the three Healthboard areas

N= 982		Lothian N=611	Borders N=92	Fife N=281	Chi squared
Gender	Male	326 (53%)	46 (50%)	171 (61%)	P=0.07
Age	Median	72.9yrs	71.9	72.1	P=0.9
	Range	37-93	44-90	45-93	(ANOVA)
Carstairs	1	113 (19%)	13 (14%)	26 (9%)	**P<0.001**
	2	105 (17%)	38 (41%)	35 (13%)	
	3	131 (21%)	32 (35%)	59 (21%)	
	4	179 (29%)	9 (10%)	130 (46%)	
	5	83 (14%)	0	31 (11%)	
Performance Status	0-1	242 (40%)	45 (49%)	109 (39%)	P=0.3
	2	147 (24%)	13 (14%)	61 (22%)	
	3-4	145 (24%)	23 (25%)	67 (24%)	
	Not known	77 (13%)	11 (12%)	44 (16%)	

2) Management

No record could be found of any of the unverified cases receiving any treatment for their lung cancer within the SCAN region, or on the Scottish Cancer Registry database, so it was unlikely that these patients received any type of treatment.

On review of the medical records of the 107 patients identified only by the Cancer Registry but not the SCAN audit, none were felt to have been suitable for potentially curative therapy. This group constituted mainly elderly patients admitted under the care of Medicine for the Elderly and who died within a few days of entering hospital.

Of the verified cases, thirteen were either confirmed at autopsy or died on the day they were diagnosed (3 SCLC, 8 NSCLC and 2 radiological), and as these patients would have been unable to receive any treatment they have been excluded from the analysis of management. Of the thirteen excluded cases six lived in Lothian, four in Fife and three in the Borders.

Of the remaining 971 cases, 586 (60%) underwent a bronchoscopy and 822 (85%) a CT scan. More patients living in Fife underwent a bronchoscopy; (77%) compared with those in the Borders (58%) and in Lothian (53%) (Chi-squared P<0.001), but similar numbers of patients had a CT scan (86% Fife, 90% Borders and 83% Lothian).

The method used to obtain the pathological specimen is shown in Table 6.3, along with the distribution of pathological subtypes and stage distribution at presentation. In Fife 22% of patients did not have pathological confirmation compared with 34% in Borders and 28% in Lothian, but this difference was non-significant (Chi-squared P=0.09).

In Fife, 48% of patients presented with metastatic disease, 32% regional disease, 10% localised disease and the stage was unknown for 10%. The stage distribution at presentation for Lothian was 41%, 35%, 15% and 10%, and for Borders 36%, 42%, 9% and 14%, respectively. However, these differences are not statistically significant (Chi-squared P=0.1). (see also Appendix 4)

Details of the treatment delivered to patients with the different pathological types of cancer are shown in Table 6.4.

'Potentially curative therapy' was delivered to 229 (23.6%) patients; 102 underwent a resection, 101 radical radiotherapy, and 26 chemo-radiation for limited stage SCLC. Palliative treatment was delivered to 39% of patients (236 palliative radiotherapy only, 91 chemotherapy only and 49 both), and 366 (38%) received no treatment.

Two patients died within a month of surgery (2% post-operative mortality), eight within a month of starting chemotherapy (5 NSCLC (5.6%) and 3 SCLC (3.4%)) and 60 (28%) within a month of palliative radiotherapy.

Table 6.3 Management and tumour characteristics

		(N=971)
Procedure for pathology	Bronchoscopy	350 (36%)
	Needle biopsy of primary	173 (18%)
	Lymph node	13 (1%)
	Pleural aspiration/biopsy	28 (3%)
	Sputum	11 (1%)
	Surgical procedure	28 (3%)
	Other	48 (5%)
	Unknown	62 (6%)
	Radiology only	258 (27%)
Pathological type	Squamous	223 (23%)
	Adenocarcinoma	174 (18%)
	NSCLC NOS	148 (16%)
	Other NSCLC	27 (3%)
	SCLC	141 (15%)
	No pathology	258 (26%)
NSCLC / No pathology[1] N=830	Stage IA	37 (4%)
	IB	87 (10%)
	IIA	8 (1%)
	IIB	55 (7%)
	IIIA	96 (11%)
	IIIB	111 (13%)
	IV	332 (40%)
	Localised	8 (1%)
	Regional	16 (2%)
	Unknown	80 (10%)
SCLC Stage N=141	Limited	53 (38%)
	Extensive	79 (56%)
	Unknown	9 (6%)

[1]Pathological stage if surgery performed, otherwise clinical staging

Table 6.4 Management broken down by pathological type

NSCLC N=572	Surgery only	78 (14%)
	Surgery and post-operative radiotherapy	19 (3%)
	Surgery and chemotherapy	2 (0.3%)
	Surgery and palliative radiotherapy	2 (0.3%)
	Radical radiotherapy	50 (9%)
	Radical radiotherapy and chemotherapy	27 (5%)
	Palliative radiotherapy	174 (30%)
	Palliative radiotherapy and chemotherapy	32 (6%)
	Chemotherapy	39 (7%)
	None	149 (26%)
SCLC N=141	Surgery and chemotherapy	1 (1%)
	Chemotherapy and adjuvant radiotherapy	26 (18%)
	Palliative radiotherapy	10 (7%)
	Palliative radiotherapy and chemotherapy	17 (12%)
	Chemotherapy	52 (36%)
	None	38 (26%)
No pathology N=258	Radical radiotherapy	24 (9%)
	Palliative radiotherapy	52 (20%)
	None	184 (71%)

Three SCLC cases (2%) and 20 (3.5%) NSCLC cases entered therapeutic clinical trials.

There was a significantly lower use of 'any treatment', and of 'potentially curative treatment' in patients from Fife when compared with those from Lothian and Borders healthboard areas (see Table 6.5). The difference in the use of 'potentially curative treatment' was primarily due to more use of radical radiotherapy; Lothian 91 patients (15%), Borders 16 (18%) and Fife 20 (7%).

Table 6.5 Treatment intent broken down by healthboard area

	Lothian (n=605)	Borders	Fife	Chi-squared
Any treatment	393 (66%)	58 (65%)	151 (55%)	P=0.007
Potentially curative treatment	61 (27%)	24 (27%)	44 (16%)	P=0.002
Surgery	70 (12%)	8 (9%)	24 (9%)	P=0.38
Radiotherapy	278 (46%)	48 (54%)	107 (39%)	P=0.002
Chemotherapy	133 (22%)	17 (19%)	46 (17%)	P=0.12

In a logistic regression model the adjusted odds of patients in Fife receiving any treatment was 0.5 (0.3-0.7) that of Lothian patients and potentially curative treatment 0.3(0.2-0.7) (see Table 6.6). Poor performance status, age over 80, lack of histological confirmation, and more advanced stage were also associated with reduced odds of receiving 'any treatment'.

Similar factors were also associated with reduced odds of receiving 'potentially curative treatment', with those aged over 70 also less likely to undergo this type of treatment.

Deprivation had no impact on delivery of any treatment, nor potentially curative treatment.

Table 6.6 Univariate and multivariate analysis of factors affecting use of 'any treatment' and 'potentially curative' treatment (PCT)

	Any treatment	χ^2 P value	Unadjusted odds any treatment	Adjusted odds of any treatment	PCT	χ^2 P value	Unadjusted odds of PCT	Adjusted odds of PCT
Male	334 (62%)	0.95	1	1	132 (25%)	0.45	1	1
Female	271 (62%)		1.0(0.8-1.3)	1.0(0.7-1.0)	97 (22%)		0.9(0.7-1.2)	0.7(0.4-1.1)
<60	110 (97%)	**<0.001**	1	1	47 (36%)	**<0.001**	1	1
60-69	184 (75%)		**0.6(0.3-0.98)**	0.9 (0.5-1.7)	78 (32%)		**0.8(0.5-1.3)**	0.7 (0.4-1.4)
70-79	244 (59%)		**0.3(0.2-0.5)**	0.6 (0.3-1.0)	85 (21%)		**0.5(0.3-0.7)**	**0.4 (0.2-0.7)**
80+	67 (37%)		**0.11(0.0-0.2)**	**0.2 (0.1-0.5)**	19 (10%)		**0.2(0.1-0.4)**	**0.1 (0-0.2)**
PFS 0-1	325 (82%)	**<0.001**	1	1	167 (42%)	**<0.001**	1	1
2	144 (65%)		**0.4(0.3-0.5)**	**0.5 (0.3-0.8)**	34 (16%)		**0.3(0.2-0.4)**	**0.3 (0.2-0.5)**
3-4	89 (39%)		**0.16(0.1-0.2)**	**0.2 (0.1-0.3)**	11 (5%)		**0.1(0-0.13)**	**0.1 (0.05-0.3)**
Unknown	47 (37%)		**0.13(0.1-0.3)**	**0.3 (0.2-0.6)**	17 (13%)		**0.2(0.1-0.4)**	0.8 (0.3-2.)
Carstairs 1	99 (66%)	0.71	1	1	42 (28%)	0.21	1	1
2	109 (62%)		0.8(0.5-1.3)	0.7(0.4-1.3)	32 (18%)		**0.6(0.3-0.96)**	0.5(0.2-1.05)
3	130 (60%)		0.8(0.5-1.2)	0.8(0.4-1.4)	51 (24%)		0.8(0.5-0.13)	0.7(0.3-1.9)
4	193 (61%)		0.8(0.5-1.2)	0.9(0.5-1.5)	72 (23%)		0.8(0.5-0.12)	09(0.5-1.8)
5	74 (65%)		0.9(0.6-1.6)	1.2(0.6-.5)	32 (28%)		1.0(0.6-1.7)	1.0(0.4-2.3)
Lothian	396 (65%)	0.007	1	1	161 (27%)	0.002	1	1
Borders	58 (65%)		1.0(0.6-1.6)	1.2 (0.6-2.3)	24 (27%)		1.1(0.6-1.7)	1.2 (0.6-2.4)
Fife	151 (55%)		**0.6(0.5-0.8)**	**0.5 (0.3-0.7)**	44 (16%)		**0.5(0.4-0.8)**	**0.3 (0.2-0.7)**
NSCLC	423 (74%)	<0.001	1	1	178 (31%)	<0.001	1	1
SCLC	106 (75%)		1.1(0.7-1.6)	1.6 (0.95-2.8)	27 (19%)		**0.5(0.3-0.8)**	1.0 (0.5-2.0)
No path	76 (29%)		**0.15(0.1-0.2)**	**0.2 (0.2-0.4)**	24 (9%)		**0.3(0.1-0.4)**	**0.3 (0.1-0.6)**
Localised	105 (85%)	<0.001	1	1	95 (77%)	<0.001	1	1
Regional	259 (76%)		0.8(0.5-1.4)	**0.5 (0.3-0.9)**	127 (38%)		**0.2(0.15-0.4)**	**0.1 (0.05-0.2)**
Metastatic	240 (58%)		**0.4(0.2-0.60**	**0.3 (0.2-0.5)**	7 (2%)		**0**	**0**
Unknown	1 (1%)		**0.03(0.-0.2)**	**0.0 (0-0.03)**	0		**0**	**0**

3) Survival

For the whole cohort of 1027 patients the median overall survival was 4.6 months (4.1-5.2), with 27.4% alive at one-year and 14.0% at two-years. For those patients who had pathological confirmation the median survival was 5.6 months, with 30.8% alive at one-year and 16.9% at two-years.

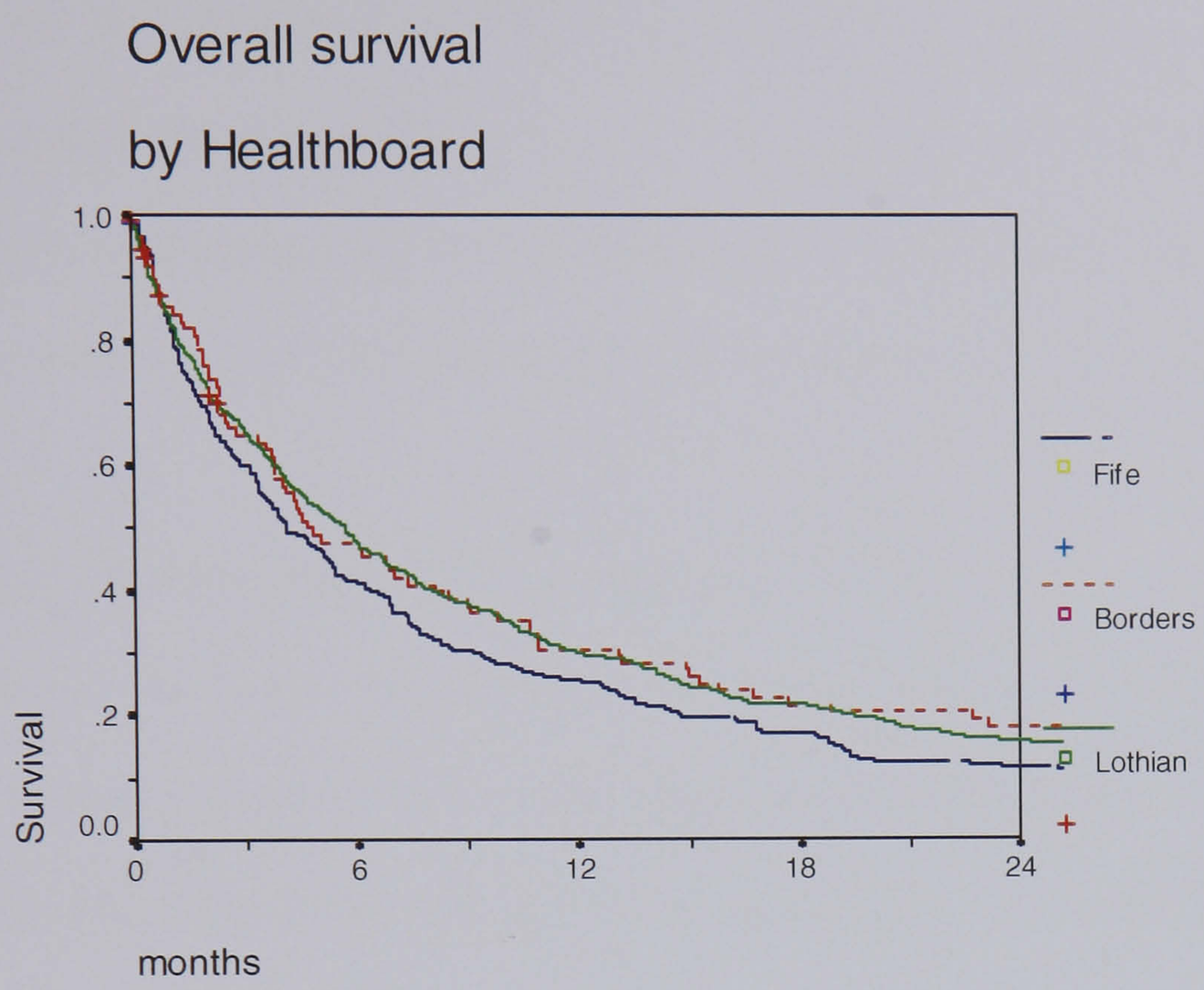
For the 971 patients whose notes could be located and who survived more than one day (similar cohort to 1995 cohort), the median survival was 5.1 months (4.5-5.7), with 28.9% alive at one year and 14.8% at two-years.

The median survival in Fife was 4.1 months(3.8-5.1) compared with 4.8months (2.4-7.3) in Borders and 5.7months (4.9-6.6) in Lothian (figure 6.1 and Table 6.7), but this was non-significant on log rank testing (P=0.07). On Cox's regression model healthboard of residence was not associated with increased hazard of death, only age over 70 (p=0.01), performance status of 2 or more (P<0.001), more advanced stage (P<0.001) were associated with increased hazard ratio of death.

Table 6.7 Survival of patients within the three healthboard areas

	N	Median survival (months)	1-year	2-year
Lothian	605	5.7 (4.9-6.6)	30%	16%
Borders	89	4.8 (2.4-7.3)	31%	18%
Fife	277	4.1 (3.1-5.1)	26%	12%

Figure 6.1 Overall survival observed in the three healthboard areas



p=0.07

Comparison with 1995 cohort

Of the 3833 patients in the 1995 Scottish lung cancer audit, 927 were diagnosed in a hospital in Lothian, Borders or Fife. In the 1995 audit the case ascertainment was lower than in 2002, therefore to ensure the cohorts were as similar as possible, only the 971 patients in 2002 whose notes could be located and lived longer than a day were included in this comparison.

Table 6.8 shows the number of cases identified by the audits compared with the number of cases on the Cancer Registry (ISD) website. It clearly demonstrates that case-ascertainment in Lothian exceeds 95% for both audits, but for the Borders was 65% in 1995 and 92% 2002, and Fife 63% in 1995 and 88% in 2002. The improved case ascertainment may have diluted the impact of service changes as the additional cases identified were more likely to be older patients with more advanced disease and were less likely to have received any treatment.

Table 6.8 Case ascertainment compared with recorded cases in Cancer registry

	1995				2002			
	Male		Female		Male		Female	
	Audit	ISD	Audit	ISD	Audit	ISD	Audit	ISD
Lothian	386	400	296	298	323	337	282	283
Borders	34	55	19	26	44	46	45	51
Fife	118	172	74	131	170	195	107	118

1) Patient and tumor characteristics

Patient and tumour characteristics are shown in Table 6.9. Due to changes in allocation of Carstairs' Index it is recommended that data from the 2001 census are used for longitudinal assessments of deprivation [98], so the up-dated Carstairs' Indices, grouped in quintiles, were applied to the 1995 cohort. Data on performance status was not available for the 1995 cohort. In 1995 only 6% of patient in these three healthboard areas lived more than one-hour's journey from Edinburgh Cancer Centre so this variable was also not included in this analysis.

Table 6.9 Patent and tumor characteristics in 1995 and 2002 cohorts

		1995	2002	
Gender	Male	538 (58%)	537 (55%)	P=0.25
Age	<60	135 (15%	131 (14%)	**P=0.002**
	60-69	298 (32%)	246 (25%)	
	70-79	359 (39%)	411 (42%)	
	80+	135 (15)	183 (19%)	
Carstairs	1	131 (14%)	149 (15%)	P=0.13
	2	155 (17%)	175 (18%)	
	3	240 (26%)	217 (22%)	
	4	258 (28%)	316 (33%)	
	5	120 (13%)[1]	114 (12%)	
	Lothian	682 (74%)	605 (62%)	**P<0.001**
	Borders	53 (6%)	89 (9%)	
	Fife	192 (21%)	277 (29%)	
Pathology	NSCLC	543 (59%)	572 (59%)	P=0.055
	SCLC	166 (18%)	141 (15%)	
	No pathology	216 (23%)	258 (27%)	
	Localised	229 (25%)	132 (14%)	**P<0.001**
	Regional	314 (34%)	339 (35%)	
	Metastatic	275 (30%)	411 (42%)	
	Unknown	109 (12%)	89 (9%)	
CT scan performed		430 (46%)	822 (85%)	**P<0.001**

[1] For 23 data missing

The increasing age of patients over the seven years reflects the ageing of the high-risk heavy smoking birth-cohorts and this trend is likely to continue over the next decade. The number of cases in Lothian reduced, but increased in Fife. This may reflect better case ascertainment in Fife as the incidence recorded by the Scottish Cancer Registry did not change in these regions over this period [98]. There was also a non-significant increase in the proportion of patients without a tissue diagnosis identified by the audit, reflecting the higher case ascertainment.

The apparent increase in the proportion of patients who presented with more advanced disease maybe have been an artifact of the increased use of CT scanning and better case ascertainment. However, if just CT-staged patients were selected there was still a significant difference; 25% of patients in 1995, and in 2002 41% presenting with metastatic disease. This could be due an increased proportion of patients with clinically obvious stage IV disease having CT scan performed for evaluation of disease prior to commencing palliative chemotherapy, or technical improvements and more experienced radiologists has resulted in higher detection of metastatic deposits.

2) Treatment

The overall proportion of patients receiving treatment did not increase in the seven years 1995 to 2002 (Table 6.10). However, though this proportion remained unchanged this was despite higher case ascertainment and an aging population.

The proportion of patients treated with curative intent increased from 14% to 24%, primarily due to a trebling of the number of people treated with radical radiotherapy. The proportion of patients treated with radiotherapy overall did not change, just that those treated were more likely to have received a curative dose.

Disappointingly there was no increase in the proportion of patients under-going resection for their lung cancer. This may simply reflect the marked co-morbidity in Scottish lung cancer patients, which precludes many lung cancer patients from having surgery.

The number of patients receiving chemotherapy increased, mainly due to doubling of the use of chemotherapy in NSCLC (7.1% 1995 v 17.5% 2002). Evidence demonstrating the benefit of palliative chemotherapy in this group was published in the mid 1990s [6, 44]. The proportion of SCLC patients receiving chemotherapy did not change, and was 65% in 1995, and 68% in 2002.

Table 6.10 Comparison of treatment intent in 1995 and 2002

	1995	2002	
Any treatment	582 (63%)	605 (62%)	P=0.85
Potentially curative	131 (14%)	229 (24%)	P<0.001
Palliative	451 (49%)	376 (39%)	
Surgery	95 (10.2%)	102 (10.5%)	P=0.88
Radiotherapy	400 (43%)	433 (45%)	P=0.55
Radical[1]	44 (4.7%)	146 (15%)	P<0.001
Palliative	356 (38%)	296 (31%)	
Chemotherapy	151 (16%)	196 (20%)	P=0.03

[1]Includes radical, PORT and chemo-radiation for L-SCLC

The changes in management by pathological subtype are shown in Table 6.11.

Table 6.11 Management for each pathological type in 1995 and 2002

		1995	2002
NSCLC	Surgery only	82 (15%)	78 (14%)
	Surgery and post-operative radiotherapy	7 (1%)	19 (3%)
	Surgery and chemotherapy	1 (0.2%)	2 (0.3)
	Surgery and palliative radiotherapy	2 (0.4%)	2 (0.3%)
	Radical radiotherapy	18 (3.3%)	50 (8.7%)
	Radical radiotherapy and chemotherapy	1 (0.2%)	27 (4.7%)
	Palliative radiotherapy	219 (40.5%)	174 (30.4%)
	Palliative radiotherapy and chemotherapy	20 (4%)	32 (5.6%)
	Chemotherapy	17 (3%)	39 (6.8%)
	None	176 (32.4%)	149 (26%)
SCLC	Surgery and chemotherapy +/-RT	1 (0.5%)	1 (0.5%)
	Chemotherapy and adjuvant radiotherapy	12 (7%)	26 (18%)
	Palliative radiotherapy	17 (10%)	10 (7%)
	Palliative radiotherapy and chemotherapy	19 (11.5%)	17 (12%)
	Chemotherapy	78 (46%)	52 (37%)
	None	39 (23%)	35 (25%)
No pathology	Radical radiotherapy	5 (2%)	24 (9%)
	Palliative radiotherapy	79 (38%)	52 (20%)
	None	130 (60%)	182 (71%)

To investigate further the factors that affected the use treatment and potentially curative treatment a multivariate analysis was performed and is shown in Table 6.12.

Table 6.12 Factors affecting the use of 'any treatment' and 'potentially curative treatment'

	Unadjusted odds of treatment	Adjusted odds of treatment	Unadjusted odds of PCT	Adjusted odds of PCT
Male	1	1	1	1
Female	0.9(0.8-1.1)	0.9(0.7-1.1)	1.0(0.8-1.2)	0.9(0.7-1.2)
Age <60	1	1	1	1
60-69	0.6(0.4-0.8)	**0.8 (0.4-0.99)**	**0.7(0.5-0.99)**	**0.6 (0.4-0.9)**
70-79	0.3(0.2-0.4)	**0.4(0.4-0.5)**	**0.4(0.3-0.5)**	**0.3 (02-0.4)**
80+	**0.1(0.06-0.13)**	**0.1 (0.08-0.2)**	**0.1(0.08-0.2)**	**0.1 (0.03-0.1)**
Carstairs 1	1	1	1	1
2	1.9(0.8-1.5)	1.0(0.7-1.5)	0.7(0.5-1.1)	0.7(0.4-1.1)
3	1.0(0.7-1.4)	0.9(0.6-1.3)	0.7(0.5-1.1)	0.7(0.4-1.1)
4	0.9(0.7-1.2)	0.9(0.6-1.3)	0.7(0.5-1.0)	0.6(0.4-1.4)
5	1.1(0.7-1.5)	1.0(0.6-1.5)	0.8(0.5-1.2)	0.6(03-1.04)
Lothian	1	1	1	1
Borders	1.10.8-1.6)	1.3 (0.8-2.0)	0.8(0.5-1.3)	0.6 (0.4-1.1)
Fife	**0.7(0.6-0.8)**	**0.7 (0.5-0.9)**	**0.6(0.4-0.8)**	**0.5 (0.3-0.7)**
NSCLC	1	1	1	1
SCLC	**1.3(1.0-1.7)**	**1.8 (1.3-2.5)**	**0.5(0.3-0.4)**	**1.3(0.8-2.0)**
No pathology	0.2(0.1-0.3)	**0.3 (0.2-0.4)**	**0.2(0.1-0.3)**	**0.2(0.1-0.4)**
Localised	1	1	1	1
Regional	0.9(0.7-1.3)	0.7 (0.5-1.0)	**0.590.4-0.6)**	**0.6 (0.4-0.9)**
Metastatic	**0.5(0.3-0.6)**	**0.3 (0.2-0.5)**	**0.01(0-0.03)**	**0.004(0)**
Unknown	0.07(0-0.1)	**0.08 (0-0.13)**	0	**0**
1995	1	1	1	1
2002	**1.0(0.8-1.2)**	**1.3 (1.1-1.7)**	**1.8(1.5-2.4)**	**6.0 (4.3-8.4)**

Even after adjusting for other factors, patients diagnosed in 2002 were significantly more likely to receive 'any treatment' and 'potentially curative treatment' than those diagnosed in 1995. Older patients, those without pathological confirmation, metastatic disease and patients living in Fife were also less likely to receive 'any treatment' and 'potentially curative treatment'.

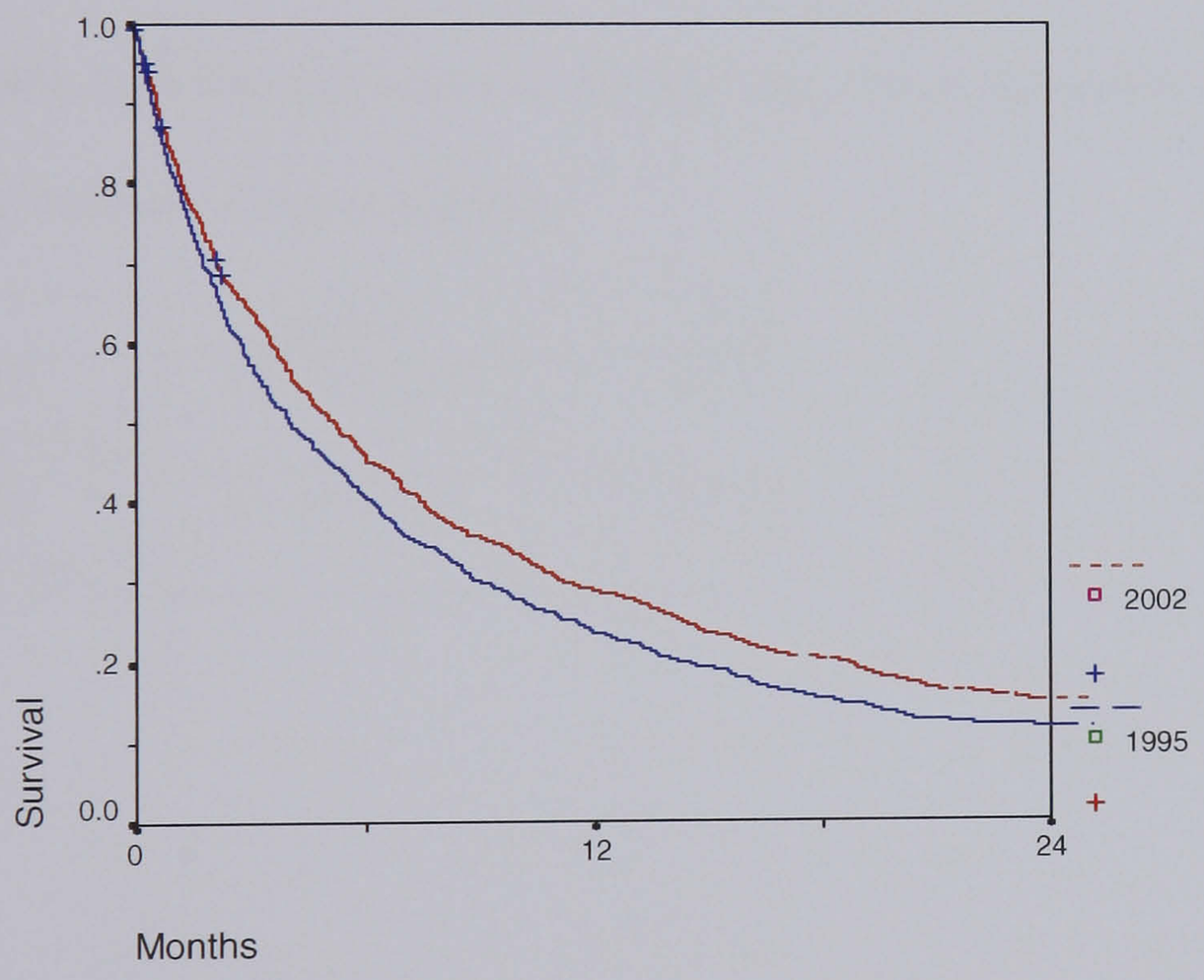
3) Survival

The median overall survival for lung cancer in Lothian, Borders and Fife increased from 4.1 months to 5.1 months in the seven years from 1995 to 2002 (see Table 6.13 and figure 6.2).

Table 6.13 Survival in South East Scotland 1995 v 2002

	Median	1 yr	2 yr	Log rank
1995 (n=927)	4.1 (3.5-4.6)	23.4% (20.7-26.1)	11.4% (9.3-13.5)	P=0.0029
2002 (n=971)	5.1 (4.5-5.8)	28.9% (26.1-31.8)	14.8% (12.5-17.1)	

Figure 6.2 Overall survival by year of diagnosis



p=0.0029

To investigate the impact of the improved case ascertainment, the Cancer Registry also provided data on the eligible cases from the 1995 audit that had been excluded because the medical records could not be found. There were 61 patients including 35 men and the median age was 75 (range 34-92). Over half this group (54%) died on the day they were diagnosed. Though of the remainder, eight lived more than six months.

The survival of the whole population cohort of 994 patients diagnosed in 1995 and 1027 patients from 2002 was then calculated. The improved survival remained significant. (Table 6.14)

Table 6.14 Overall survival for all lung cancer patients from South East Scotland in the Scottish Cancer registry

	Median	1 yr	2 yr	Log rank
1995 (n=994)	3.6 (3.1-4.1)	22.4%	10.8%	P=0.003
2002 (n=1027)	4.6 (4.1-5.2)	27.4%	14.0%	

Reasons for the improvement in survival

To explore whether the improvement in survival observed was not simply due to changes in patient and tumour characteristics rather than the impact of increased use of treatment, a Cox's regression model analysis was performed (Table 6.15). This demonstrated that even when the differences in age and stage are taken into account patients diagnosed in 2002 had a hazard ratio of death 0.7 (0.6-0.8) compared with patients diagnosed in 1995.

Table 6.15 Factors affecting hazard of death

	Unadjusted hazard of death	Adjusted hazard of death
Male	1	1
Female	0.9(0.8-1.0)	0.9(0.8-1.02)
Age <60	1	1
60-69	1.2(1.0-1.4)	**1.2 (1.04-1.5)**
70-79	**1.6(1.3-1.8)**	**1.6 (1.3-1.8)**
80+	**1.9(1.6-2.2)**	**1.8 (1.5-2.2)**
Carstairs 1	1	1
2	1.2(1.0-1.4)	1.2(1.0-1.42)
3	1.1(0.9-1.3)	1.1(1.0-1.3)
4	1.2(1.0-1.4)	**1.2(1.04-1.4)**
5	1.1(0.9-1.3)	1.2(1.0-1.4)
Lothian	**1**	1
Borders	**1.0(0.8-1.2)**	1.0(0.8-1.2)
Fife	**1.2(1.1-1.3)**	1.1(0.9-1.2)
NSCLC	**1**	1
SCLC	**1.4(1.2-1.5)**	1.0 (0.8-1.1)
No pathology	**1.8(1.6-2.0)**	**1.4(1.2-1.6)**
Localised	1	1
Regional	**1.7(1.5-2.0)**	**1.9 (1.6-2.3)**
Metastatic	**3.7(3.2-4.3)**	**4.2 (3.6-4.8)**
Unknown	**4.3(3.5-5.2)**	**3.6 (2.9-4.4)**
1995	**1**	**1**
2002	**0.9(0.8-0.95)**	**0.7 (0.6-0.8)**

There was no change in the overall survival following surgery (2 year overall survival 77% 1995 v 81% 2002 log rank p=0.99), radical radiotherapy (2-year overall survival 70% v 67% log rank p=0.97) or palliative chemotherapy (1-year overall survival 25% v 24% log rank p=0.42). The latter two were reassuring because despite more patients receiving these treatments, a similar proportion benefited.

There was a slight decline in the median survival of patients undergoing palliative radiotherapy (5.2 to 4.4months log rank p=0.03), probably due to changes in patient selection. In 2002 palliative radiotherapy was only used for patients unsuitable for either radical radiotherapy or palliative chemotherapy.

If the Cox' proportional hazards model was repeated with the addition of the variable 'treatment intent' (PCT v palliative v none) the hazard of death was still lower in 2002 compared with 1995 (HR 0.8 (0.7-0.9)) suggesting that it was not just the increased use of potentially curative therapy that was responsible for the improved outcome.

SUMMARY OF RESULTS

- Patients diagnosed in 2002 were older than those in 1995
- There appeared to be more patients diagnosed with metastatic disease in 2002, but this could have been an artifact of higher case ascertainment and more patients undergoing a CT scan.
- The absolute proportion of patients treated did not change, but twice as many were treated with curative intent in 2002 than 1995.
- The proportion of patients treated with radical radiotherapy increased from 5% to 15%, but the proportion undergoing surgery remained unchanged at 10%
- The use of chemotherapy for NSCLC increased from 7% to 17% of patients
- On multivariate analysis the odds ratio of receiving 'any treatment' in 2002 was 1.3 and the odds ratio of receiving 'potentially curative treatment' was 6.0 in 2002 compared with 1995
- Patients diagnosed in 2002 had significantly longer survival with the median survival increasing from 4.1 months to 5.1 months.
- On Cox's regression model the hazard ratio of dying within two years was 0.7 in 2002 compared with 1995.
- The improvement in survival was only partly due to increased use of radical radiotherapy therefore other, unidentified, factors appear to also be important.

CHAPTER 7

Optimal treatment utilisation and resources for the treatment of lung cancer in South-East Scotland

Introduction

As has been shown in the previous chapters, one of the reasons for poor survival of lung cancer patients in Scotland has been under-use of treatment. Though the number of patients receiving radical radiotherapy and chemotherapy for NSCLC has increased markedly, is there still under utilisation of treatment?

The potential reasons for the under-use of treatment are complex, but include nihilism on the part of clinicians [185], a fatalistic attitude of some lung cancer patients, and lack of resources.

Therapeutic nihilism by clinicians can be overcome by site specialisation and multi-disciplinary team working, which attracts motivated clinicians with a special interest in lung cancer and a desire to in improve the outcomes [125]. The impact of the use of treatment guidelines, such as SIGN guidelines, is more difficult to establish. In the previous study examining the introduction of protocols in the management of SCLC in BC, the number of patients receiving appropriate treatment increased, but did not result in a statistically significant improvement in survival [113]

Patients with lung cancer tend to be more fatalistic than those with other primary tumours, such as breast cancer; expecting much greater survival benefit for toxicities experienced [179]. Therefore it is not uncommon for patients to decline curative treatment with surgery or radical radiotherapy, or palliative chemotherapy. Though often, with good communication and patient education by lung cancer specialists, this patient nihilism and prejudice against treatment can be overcome.

However, it is paramount that when treatments have been proven to be of cost-effective benefit to patients' outcome, in terms of both survival and quality of life, that sufficient resources are in place to meet the demand.

Data from EUROCARE and Royal College of Radiologists audits have suggested that the poor outcome in the UK might be due to lack of oncologists and radiotherapy equipment [8]. The Royal College of Radiologists recommends that there are 5.0 radiotherapy machines per million head of population, and the ESTRO QUARTS European model suggested 6.2 machines per million are required for England [15]. In 1995, Scotland had 4.0 machines per million, and in 2002 4.5 per million. There is an on-going program of installing new machines to bring the capacity up to 5.0 machines per million by the end of 2007, but with a predicted 18% increase in the number of cancer cases (mainly breast, colon and prostate) over the next decade further expansion will be required to keep pace with this demand [174].

Not only are radiotherapy machines in short supply, but also crucial staff particularly therapeutic radiographers and radiation physicists. There is an international shortage of these specialists, and in 2002 most Scottish radiotherapy departments had vacancies.

Though radiotherapy is the most frequently used treatment modality in lung cancer, it is also important to have sufficient surgical capacity, and the resources, both financial and organisational, to delivery chemotherapy to all patients for whom it might be of benefit.

In order to plan for the future it is important to know what level of resources should be in place to meet the demand were treatment to be optimal. Therefore a model was developed to:-

a) Assess the gap between current actual and optimal delivery

b) Provide information on current resource requirements

Methods

Indications for treatment

As discussed in Chapter 1, there are clearly defined indications for surgery, radiotherapy, and chemotherapy in the treatment of patients with lung cancer. The principal determinants of treatment selection are pathological type, stage, and the performance status of the patient. Some patients elect not to have the treatment recommended, but the resources to be able to offer all patients the best treatment for their clinical situation should be available.

Obviously there are some areas of clinical controversy. However, as this analysis applies to South-East Scotland the current interpretation of the data and regimens delivered by the Edinburgh Cancer Centre Lung Cancer Team (which are based on the SIGN and NICE guidelines) were used for this model, and are set out in Table 7.1.

Table 7.1 Indications for treatment used in the models

Treatment	Scenario	Details
Surgery	Stage I or II NSCLC PFS 0-1	Pneumonectomy or lobectomy
Radical radiotherapy	Stage I-II NSCLC PFS 0-1 medically unfit for surgery (FEV1 <1L) or Stage I or II NSCLC PFS 2	Either 54Gy in 36 fractions (CHART) or 55Gy in 20 fractions
	Stage III NSCLC PFS 0-1 encompassable within safe RT volume, no cytologically proven pleural effusion.	Either 54Gy in 36 fractions (CHART), 55Gy in 20 fractions or 60-66Gy in 30-33 fractions with chemotherapy
Adjuvant radiotherapy + prophylactic cranial radiotherapy (PCI)	L-SCLC PFS0-2	50Gy in 20 fractions + 30Gy in 10 fractions PCI
Post-operative radiotherapy	Positive resection margin	55Gy in 20 fractions
Palliative radiotherapy	Stage I-III NSCLC / L-SCLC PFS 3-4 with local symptoms	Either 20Gy in 5 fractions or 10Gy in 1 fraction
	Stage III NSCLC PFS 0-1 not encompassable within safe radiotherapy volume, no effusion	39Gy in 13 fractions
	Stage IIIB (pleural effusion) or IV NSCLC/ E-SCLC with focal chest symptoms PFS 0-3	Either 20Gy in 5 fractions or 10Gy in 1 fraction
	Stage IV NSCLC symptomatic brain metastases PFS 0-2, ESCLC brain metastases PFS 0-3	Either 20Gy in 5 fractions or 12Gy in 2 fractions
	Stage IV NSCLC / E-SCLC symptomatic bone metastases PFS 0-3	Either 20Gy in 5 fractions or 8Gy in 1 fraction
Chemotherapy	Pathological Stage II-III PFS 0-1 post-operative adjuvant	4 cycles of cisplatin vinorelbine
	L-SCLC PFS 0-3	4 cycles cisplatin/carboplatin & etoposide
	Stage III NSCLC PFS 0-1 chemo-radiation	4 cycles of cisplatin & vinorelbine or 3 cycles carboplatin & gemcitabine
	Stage IIIB (pleural effusion) or Stage IV NSCLC PFS 0-1 palliative chemotherapy	4 cycles of gemcitabine & carboplatin
	Stage IV NSCLC PFS 2 age <60 palliative chemotherapy	4 cycles of gemcitabine & carboplatin
	E-SCLC PFS 0-2	6 cycles carboplatin and etoposide

Areas of controversy include:

i) Definition of medically inoperable

Not all patients are medically fit for surgery. The most frequent reasons are poor lung function due to chronic obstructive pulmonary disease, and cardiovascular disease. The criteria for deciding whether or not a patient is unfit for surgery in the basis of their heart disease are fairly subjective, but it is generally accepted that patients with an FEV1 of less than one litre are unlikely to tolerate surgery. FEV1 is a measure of the volume of air a patient can exhale over a second, and is usually in the region of 2-3 litres. A number of studies have investigated the association between either the percentage of predicted or absolute value of FEV1 and the risk of post-operative complications [126]. The percentage of predicted pulmonary function is a better predictor of outcome [17], but these values were not recorded in the audit database with sufficient frequency. Therefore a level below 1L/second was used to define a 'medically inoperable' threshold. In a case-series of surgical patients from Papworth hospital, 50 patients (45%) had an FEV1 below the standard thresholds of 1.5L for lobectomy and 2.0L for pneumonectomy, but none had an FEV1 of less than 1L [206].

ii) Surgery for Stage III NSCLC with single nodal group involvement.

Though this is it routinely offered in some centres in the US the efficacy of this treatment remains debated, and in the UK is still considered experimental [195].

iii) Post-operative radiotherapy in patients found to have mediastinal nodal involvement

This has not been proven to improve survival, and may actually be detrimental in some patients [151], so post-operative radiotherapy is not routinely offered to patients, unless there is doubt about the resection margin.

iv) Use of radical radiotherapy in frailer (performance status 2 (PFS 2)) NSCLC patients

In South East Scotland the majority of patients in this group are offered this treatment, unless their performance status is declining fast as a consequence of their cancer.

v) Use of chemotherapy in frailer (PFS 2) patients with Stage IV disease.

Patients with borderline performance status derive less benefit from chemotherapy than fit patients [20]. For purposes of this analysis a cut-off of age under sixty was used to ascertain the proportion of patients with PFS 2 suitable for chemotherapy. Though no such dogmatic age limit is applied in everyday clinical practice, if frail patients are offered chemotherapy it more is likely that they will be in the youngest age category.

The models only include treatments delivered as part of the 'initial treatment package' to enable comparison with the data on actual treatment delivered.

Establishing proportion of patients suitable for each treatment indication

i) Distribution of stage and performance status in lung cancer patients from South East Scotland

Once the indications for each treatment were defined, prospectively collected data on stage and performance status within the population were used to calculate the proportion of patents fitting each clinical scenario. In order to ensure up-to-date figures, data from patients diagnosed with lung cancer in the SCAN region in 2004 were used for this model. The introduction of electronic data capture at the multi-disciplinary meetings has enabled greater completeness of data collection.

In 2004, the SCAN prospective audit identified 1053 patients, 615 from Lothian, 82 Borders, 256 Fife and 100 Dumfries and Galloway diagnosed with lung cancer; corresponding to 91.4% case ascertainment when compared to Scottish Cancer Registry average for period 1999-2003.

The median age was 71.6 years with a range of 37-97 years. Detailed staging information was available for 92% patients and performance status for 82%.

The distribution of stage and pathological type by the health boards is shown in Table 7.2, along with performance stage distribution by stage.

Table7.2 Distribution of stage and performance status

		Lothian	Borders	Fife	D&G	Total	Performance Status by Stage			
							0-1	2	3-4	?
NSCLC (n=676)	Stage I-II	98	17	26	14	23%	73%	11%	3%	13%
	Stage III	154	19	43	15	34%	63%	22%	9%	6%
	Stage IV	141	19	79	22	39%	44%	20%	20%	16%
	Unknown	13	1	5	10	4%	13%	7%	10%	70%
SCLC (n=163)	Limited	36	2	13	9	37%	82%	12%	3%	3%
	Extensive	50	5	29	11	59%	35%	26%	19%	20%
	Unknown	2	1	1	4	4%	0%	14%	0%	86%
No path (n=214)	Stage I-II	24	3	8	1	17%	36%	33%	28%	3%
	Stage III	35	2	13	2	24%	10%	16%	51%	23%
	Stage IV	38	4	32	6	37%	18%	17%	39%	27%
	Unknown	24	9	7	6	22%	15%	6%	19%	60%

These data were then used to calculate the number of patients eligible for each treatment. In order to include all patients, those with NSCLC and no pathology were combined to make one group 'not-SCLC' and then the patients without stage or without performance status recorded were re-distributed according to the ratio of the known cases (Table 7.3a).

Table 7.3a Performance status by stage for 2004 SCAN

2004				PFS0-1	PFS 2	PFS 3	PFS 4
Not – SCLC	84%	Stage I or II	23%	74%	18%	7%	1%
		Stage III	35%	56%	23%	14%	7%
		Stage IV	42%	44%	23%	23%	10%
SCLC	16%	Limited stage	39%	82%	14%	4%	0%
		Extensive	61%	44%	33%	19%	4%

This process was also performed on the 2002 data (after having excluded the unverified patients and those living <1day as these would not have been able to receive treatment). However, 13% of patients did not have their performance status recorded, and for 12% the stage was unknown or identified only as local or regional. The higher proportion of patients without a defined category makes the proportions less accurate (Table 7.3b), so the 2004 model was selected for use in the models.

Table 7.3b Performance status by stage for 2002 SCAN

2002				PFS0-1	PFS 2	PFS 3	PFS 4
Not – SCLC	85%	Stage I or II	25%	68%	19%	11%	2%
		Stage III	29%	47%	31%	18%	4%
		Stage IV	46%	33%	26%	29%	12%
SCLC	15%	Limited stage	40%	62%	27%	11%	0%
		Extensive	60%	40%	30%	19%	11%

ii) Establishing other factors involved in management decisions

a) Proportion requiring surgery

The proportion of patients with early stage and a good performance status has been established by the method above, but it was also necessary to estimate the proportion of patients who were medically inoperable.

Therefore, in order establish the proportion of patients with poor pulmonary function and an FEV1 below the 1L threshold, the data on pulmonary function tests from Lothian in the 2004 cohort were examined. These data were available for 408 of the 608 patients (66%). For the patients with early stage disease, 26% had an FEV1 of <1L so would not have met the threshold for surgery. This proportion is similar to the 30% of patients turned down for surgery on grounds of poor pulmonary function in a hospital-based series from Northern England (11/37 Stage I-II patients), but much higher than in an Italian hospital-based series where 8% (4/53) were not operated on because of COPD[95], and in a Dutch population where 5% of Stage I and II patients had an FEV1 of less than one litre [48].

b) Proportion of patients requiring radiotherapy

i) Proportion of suitable for radical radiotherapy

Estimating the proportion suitable for radical radiotherapy with early stage disease was fairly straightforward, but assessing the proportion of patients with Stage III disease more difficult. Stage III NSCLC encompasses a wide range of disease states; including tumours where the primary and involved lymph nodes are adjacent, and others where the primary may be many centimeters from the enlarged lymph nodes. The main acute toxicities of radical radiotherapy are pneumonitis and oesophagitis, both of which are volume dependant, so the geographical distribution of the disease may preclude radical radiotherapy, even if there has been a good response to neo-adjuvant chemotherapy. The proportion of patients that do not have disease 'encompassable within a radical radiotherapy volume' is highly subjective, depending on the experience of the staff that plan the radiotherapy treatment, and the risks the oncologist and patient are prepared to take. No exact figures exist on the proportion of patients in this group, but in 2004 in SCAN 13% of good performance status Stage III patients were treated with high dose palliative radiotherapy rather than radical radiotherapy, suggesting that for the Edinburgh Cancer Centre they met these criteria.

Stage III also includes patients with a cytologically proven pleural effusion, which, regardless of the configuration of the other disease, makes the disease incurable. The proportion of patients presenting with a pleural effusion is not recorded separately in the SCAN audit database, but can be estimated. In 2004, 49 of the 127 patients with Stage III disease and PFS 0-1 had T4 disease. If the patients treated with either radical or high dose radiotherapy

were excluded (as these patients would not have had an effusion) a total of 25/127 or 20% probably had a pleural effusion at time of presentation

ii) Proportion needing post-operative radiotherapy for positive margins

Two previous models of optimal radiotherapy utilisation have been developed, and both the Canadian [197] and the Australian [49] models suggested that 2% of patients undergoing a lung cancer surgery will have positive resection margin. However, a recent Norwegian population-based study of over 3211 surgical patients 6% had an involved resection margin [188]. In the period 1994-2003 a total of 137 patients were referred to the Edinburgh Cancer Centre for consideration of post-operative radiotherapy, of these 51 had positive or uncertain resection margins. Based on an average of 110 resections per annum (100 in Edinburgh and 10 in Glasgow from D&G) the Norwegian figure of 6% appears equally applicable to Scotland.

iii) Proportion requiring palliative radiotherapy

a) Chest symptoms

Though the data on symptoms at time of presentation were recorded in the SCAN audit database, this was not sufficient completeness to use these data for the model. In the 1995 audit, 64% of patients had chest symptoms (20% haemoptysis, 25% chest pain, 48% cough) that could have benefited from thoracic radiotherapy [62]. In an analysis of 247 patients presenting to general practice with lung cancer in Devon, 20% had haemoptysis, 42% chest pain and 65% cough [85]. The Canadian model of optimal radiotherapy utilisation also used a figure of 64% for Stage III patients [197], but a lower one of 38% for Stage IV patients. In the Australian model of optimal radiotherapy use in lung cancer, Delaney *et al* used data

from three of the British 'chemotherapy versus best-supportive care' trials in which 56-71% of patients had thoracic symptoms [49]. Therefore, it appeared that the 1995 rate of 64% was a reasonable proportion to use.

However, there was no indication as to the severity of these symptoms, and chemotherapy is also beneficial for thoracic symptoms. Therefore sometimes, if the patient has widespread metastases or marked systemic symptoms, such as fatigue, then chemotherapy is used in preference to radiotherapy. It was impossible to model this subjective decision so the model will over-estimate the optimal use of radiotherapy for this group of patients.

b) Brain metastases

In a recent an analysis of the Maastricht Cancer Registry 6.8% of NSCLC and 11.2% SCLC were diagnosed with brain metastases within a month of diagnosis [172]. A review of all patients diagnosed with cancer in the Detroit area suggested that 19.9% of lung cancer patients in the SEER database were found to have brain metastases [13]. It is difficult to ascertain in this series at which time point this diagnosis was made, so the Dutch figures were used for the model.

Frail patients with brain metastases do not benefit from whole brain radiotherapy [116]. Therefore, for the model only patients with a performance status 0-2 were deemed fit for radiotherapy for NSCLC brain metastases, and because of the increased radio-sensitivity the broader group of PFS 0-3 was used for SCLC.

c) Bone metastases

There are few data examining the number of patients presenting with symptomatic bone metastases. In one hospital series from the University of Michigan 36% of patients with Stage IV NSCLC presented with bone metastases [156]. In a similar series from the Henry Ford Health System tumour database 23% of patients with stage IV disease presented with 'extra-thoracic' pain [192]. Therefore an estimate of 30% of patients with Stage IV having symptomatic bone metastases was selected.

iii) Proportion of patients requiring chemotherapy

It is recommended that chemotherapy should be delivered in the following scenarios:

i) Patients with a good performance status with pathological Stage II or III NSCLC at surgery (adjuvant post-operative chemotherapy). In the 2004 audit, 49% of the patients who underwent a resection were found to have pathological Stage II or III disease so should have been be offered this treatment.

ii) Combined with radical radiotherapy for patients with 'dry' stage III NSCLC, the proportion of patients suitable for this treatment was established by the radiotherapy model

iii) With palliative intent to patients with 'wet' Stage III or IV NSCLC.

iv) For SCLC chemotherapy should be delivered to all patients, except those with L-SCLC performance status 4 (bed bound), or E-SCLC performance status 3 or 4.

Results

1) Surgery

The model developed is shown in Table 7.4.

1) The first column represents the proportion of all lung patients with SCLC (0.16 or 16%) and 'not SCLC' (NSCLC and no pathology) (0.84)

2) The second column the distribution of stage calculated based on 2004 data

3) Third the distribution of performance status for each stage based on 2004 data

4) The proportion of patients with early stage lung cancer and a good performance but with lung function above the defined threshold of 1L/second based on the 2004 Lothian data

5) The recommended use of surgery

6) The proportion of all lung cancer patients who should according to this model undergo surgery (0.84x0.23x0.73x0.74 = 0.104).

Table 7.4 Proportion of patients suitable for surgery based o 2004 figures

<table>
<tr><td rowspan="4">Not-SCLC
(0.84)</td><td rowspan="3">Stage I-II
(0.23)</td><td rowspan="2">PFS 0-1 (0.73)</td><td>FEV1 >1
0.74</td><td>SURGERY</td><td>0.104</td></tr>
<tr><td>FEV <1
0.26</td><td>None</td><td></td></tr>
<tr><td colspan="2">PFS 2 or more (0.37)</td><td>None</td><td></td></tr>
<tr><td colspan="3">Stage III or IV (0.77)</td><td>None</td><td></td></tr>
<tr><td>SCLC
(0.16)</td><td colspan="3"></td><td>None</td><td></td></tr>
<tr><td colspan="5">TOTAL PROPORTION</td><td>0.104</td></tr>
</table>

Therefore according to the model shown in Table 7.4, the estimated optimal surgery rate for South East Scotland was 12.4% of 'Not-SCLC' cases, or 10.4% of all lung cancer patients, which is not dissimilar to the rates identified by the 1995 and 2002 audits.

However, as the model used post-operative stage, patients who were found to have unsuspected Stage III disease at time of surgery were excluded. Despite mediastinoscopy being part of routine pre-operative staging, in SCAN in 2004, 15 of the 100 patients were found to have mediastinal nodal involvement at time of resection. If this group was included as 'pre-operative Stage I-II' patients then the optimal surgical rate would have increased to 14.1% of Not-SCLC, or 11.8% of all lung cancers.

If the 2002 figures, rather than 2004 figures, were used in the model the optimal rate of surgery was 10.7% based on pre-operative, and 12.2% on post-operative stage of all lung cancers (12.6-14.3% Not-SCLC). So confirm that according to current guidelines there is not significant under-use of surgery in South East Scotland.

ii) Radiotherapy

Table 7.5 shows the model estimating the optimal radiotherapy use in South East Scotland

Table 7.5 Proportion of patients suitable for radiotherapy based on 2004 figures

Not-SCLC (0.84)	Stage I-II (0.23)	PFS 0-1 (0.74)	FEV1 >1 (0.74)	Surgery margins clear (0.94)	None	
				Margins involved (0.06)	Post-operative	0.006
			FEV1 <1 (0.26)		Radical	0.037
		PFS 2 (0.18)			Radical	0.035
		PFS 3 (0.07)	Focal Symptoms (0.64)		Palliative	0.009
			No focal symptoms (0.36)		None	
		PFS 4 (0.01)			None	
	Stage III (0.35)	PFS 0-1 (0.56)	No effusion (0.8)	Encompassable (0.87)	Radical	0.115
				Not encompassable (0.13)	High dose palliative	0.017
			Effusion (0.2)	Focal Symptoms (0.64)	Palliative	0.021
				No focal symptoms (0.36)	No none	
		PFS 2-3 (0.37)	Focal Symptoms (0.64)		Palliative	0.069
			No focal symptoms (0.36)		None	
		PFS 4 (0.07)			None	
	Stage IV (0.42)	PFS 0-3 (0.9)	Chest symptoms (0.64)		Palliative	0.203
			No chest Symptoms (0.36)	Brain mets (0.05)	PFS 0-2 (0.67)	Palliative	0.004
					PFS 3 (0.33)	None	
				No brain mets (0.95)	Symptomatic bone mets (0.3)	Palliative	0.033
					No bone mets (0.7)	None	
		PFS 4 (0.1)			None	
SCLC (0.16)	Limited stage (0.39)	PFS 0-2 (0.96)			Chemo RT+PCI	0.060
		PFS 3 (0.04)	Focal Symptoms (0.64)		Palliative	0.002
			No focal symptoms (0.36)		None	
	Extensive stage (0.61)	PFS 0-3 (0.96)	Chest symptoms (0.64)		Palliative	0.060
			No chest Symptoms (0.36)	Brain mets (0.07)	Palliative	0.002
				No brain mets (0.93)	Symptomatic bone mets (0.3)	Palliative	0.009
					No bone mets (0.7)	None	
TOTAL PROPORTION							0.68

The model therefore suggested that 68% of patients in South East Scotland should receive radiotherapy, 66% of patients with 'not SCLC' and 86% of patients with SCLC. The optimal use of radical radiotherapy was 19% of all lung cancer patients.

Repeating the model with the 2002 data suggested that 67% of patients should receive radiotherapy, 68% not-SCLC and 81% SCLC.

These estimates far exceed the proportion of patients actually treated in either 1995 or 2002. This is either due to under-use of radiotherapy, an over-estimate by the model, or a combination of the two. The latter is the most likely.

iii) Chemotherapy

Table 7.6 Proportion of patients suitable for chemotherapy based on 2004 figures

Not SCLC (0.84)	Stage I-II (0.23)	Surgery (0.54)	Pathological Stage I (0.51)	None	
			Pathological Stage II or greater (0.49)	Chemotherapy	0.051
		No surgery (0.46)		None	
	Stage III (0.35)	PFS 0-1 (0.56)		Chemotherapy	0.165
		PFS 2-4 (0.43)		None	
	Stage IV (0.42)	PFS 0-1 (0.44)		Chemotherapy	0.155
		PFS 2 (0.23)	Age <60 (0.14)	Chemotherapy	0.011
			Age >60 (0.86)	None	
		PFS 3-4 (0.33)		None	
SCLC (0.16)	Limited stage (0.39)	PFS 0-3 (1.0)		Chemotherapy	0.062
	Extensive stage (0.61)	PFS 0-2 (0.77)		Chemotherapy	0.075
		PFS 3-4 (0.23)		None	
TOTAL PROPORTION					0.52

The model is shown in Table 7.6 and suggested that chemotherapy should be delivered to 52% of all lung cancers, 45% of cases of Not-SCLC, and 86% of cases with SCLC.

Post-operative adjuvant chemotherapy was not routine clinical practice in either 1995 or 2002, so if this scenario was excluded then the optimal use of chemotherapy would have been 47% of all lung cancer cases and 39%of NSCLC cases.

The model was then repeated using 2002 data and suggested that 43% of all patients should receive chemotherapy, 36% of patients with NSCLC (31% excluding post-operative treatment) and 82% with SCLC.

This rate is obviously much higher than the observed use of chemotherapy in 1995 and 2002. The model does not take into account the age of the patient (other than for the PFS 2 patients) and chemotherapy is rarely delivered to the very elderly because of concerns of tolerance, and frequently patient choice. If the over 80's were excluded from the model, the revised estimate was 41% of patients including post-operative chemotherapy, and 37% without.

Costs of optimal treatment

The potential costs of delivering optimal treatment are shown in Appendix 4. A detailed health economic analysis is out with the scope of this thesis, but the estimate suggests that, based on 2005 figures, the cost to the NHS of optimally managing lung cancer would be between £5.3 and £6.3 million per 1000 cases.

The gap between optimal and actual treatment

Table 7.7 shows the difference between the models and the actual treatment delivered in South East Scotland in 1995 and 2002, whole of SCAN in 2004, and for comparison BC in 1995.

Table 7.7 Gap between optimal and actual treatment

		Model 2004	Model 2002	SE Scot 1995 (n=927)	SE Scot 2002 (n=971)	SCAN 2004 (n=1053)	BC 1995 (n=2073)
Not-SCLC	Surgery (based on pre-op staging)	14%	14%	12%	12%	12%	21%
	Radical radiotherapy (excl post-op)	22%	19%	4%	15%	13%*	2%
	Palliative radiotherapy	43%	45%	42%	32%	24%	34%
	Chemotherapy (excl post-op)	39%	34%	5%	12%	19%	8%
SCLC	Chemoradiation	38%	35%	8%	18%	20%	21%
	Chemotherapy	86%	82%	66%	68%	71%	76%
	Palliative radiotherapy	43%	46%	21%	22%	15%	30%

* dropped due to higher case ascertainment in 2004 and also includes patients from Dumfries and Galloway.

The gap between the modelled optimal treatment and actual treatment delivered has narrowed over the last decade, but there still appears under-use of chemotherapy, particularly for NSCLC, and in use radical and palliative radiotherapy.

The model developed obviously has a number of weaknesses

1) Data was missing on performance status and stage in up to a fifth of patients and necessitated the extrapolation of data to the whole group. This was likely to have under-estimated the proportion of patients with metastatic disease, or very poor performance status who were less likely to be presented at the multi-disciplinary meeting.

2) Lack of data on co-morbid diseases particularly cardiovascular and cerebrovascular disease which can have a major impact on management decisions, particularly suitability for surgery.

3) Lack of published population-based data of severity of symptoms and distribution of metastases at time of presentation.

4) It was impossible to model patient choice as decisions whether or not to have treatment can be based on a myriad of physical, psychological and social factors.

Further prospective data collection on severity of symptoms at presentation, co-morbid diseases and reasons behind patient and clinician decision making is required to improve the accuracy of the models.

Summary of results

- The optimal use of surgery in South-East Scotland was not dissimilar to that observed over the last decade.
- Though the use of radical radiotherapy increased to 11.4% of the population in 2004, the model suggested that up to 19% of the population might be suitable for this treatment.
- There maybe under-use of palliative radiotherapy, but it is possible that clinicians are using chemotherapy instead to palliate patients who also have systemic symptoms and to prolong survival.
- Though the use of chemotherapy has increased markedly in the last decade, there appeared to still be under-use in patients with Stage IV NSCLC, though this may reflect patient choice or other co-morbid conditions, such as, ischemic heart disease which make the use of chemotherapy more hazardous.
- If optimal treatment were delivered then around 35% of patients would be treated with curative intent.

CHAPTER 8

Discussion and Conclusions

Discussion

The work in this thesis demonstrates conclusively that in 1995, the survival of lung cancer patients in Scotland was inferior to that observed in British Columbia. This conclusion was reached by comparing two cohorts of patients using similar data collection and analysis techniques.

The potential reasons for poorer lung cancer survival in Scotland can be summarised as follows:

i) tumour related factors,

ii) patient related factors and

iii) availability and use of treatment.

1) Tumour related factors

i) Tumour pathology

The proportion of patients with different pathological sub-types was statistically significantly different between BC and Scotland. Primarily, this was due to fewer patients in Scotland having a tissue diagnosis (74% v 89%). In both populations approximately 15% of patients had small cell lung cancer. However, within the pathologically confirmed NSCLC patients there were fewer cases of adenocarcinoma in Scotland than BC (19.5% v 34%, respectively), although this could have been due to the lower rate of pathological confirmation. In some series patients with adenocarcinoma had improved survival, particularly if they had undergone surgery. However, this was not observed in either the BC or Scottish cohort.

Consequently, it would appear that difference in pathological subtypes was not a significant factor in the inferior survival in Scotland.

ii) Tumour biology

Over the last decade a considerable amount of research effort has been spent on examining the different biological profiles of lung cancer. Techniques such as, immuno-histochemistry, proteomics, and genomics have been used to attempt to correlate any changes in biology with both tumour behaviour and outcome.

A large number of studies have been conducted to search for improved prognostic markers to use in routine immunohistochemical examination of pathological specimens. However, to date only Ki-67 (a marker of proliferating cells), p53 and Bcl-2 (both associated with programmed cell death) appear linked (albeit weakly) to prognosis. Other markers which are associated with changes in prognosis in other tumours, namely EGFR and HER2 (both regulate cell proliferation), have not however demonstrated consistent results in lung cancer patients. Other cellular changes which might prove predictive of prognosis include VEGF (regulates new vessel formation), E-cadherin and β-catenin (involved in the control of cellular adhesion), p27 and p16 (involved in cell cycle control), but these require prospective validation [213].

Genomics is the study of changes in the genetic make up of a cell, whereas proteomics examines changes in the proteins. Over the last decade, research has shown that although genetic changes are important in the development of cancer, so too are any alterations in the form or function of the regulatory cellular proteins. These changes will not be detected by

gene analysis alone. Both genomic and proteomic techniques have major advantages over immuno-histochemistry as they can examine multiple changes in a cancer cell, and hence produce profiles of clustered alterations that can predict outcome more accurately. Profiles which are predictive of a worse prognosis, were initially identified in breast cancer [199], but more recently profiles predictive of inferior outcome have been identified in adenocarcinoma [14, 75, 136] and squamous cell carcinoma of the lung [96]. Studies have also identified profiles that might predict earlier lymph node spread [211], for inferior outcome following surgery [154] and for an increased risk of metastasis [161].

Whether or not differences in the molecular profiles of lung cancer exist between BC and Scotland is unknown, but the different racial profiles of the two regions make this a possibility. One study examined variations in EGFR gene mutations in specimens from Japan, Taiwan, USA and Australia, and demonstrated that ethnicity, but not geography, was linked to EGFR mutations. However, these changes were not prognostic [177].

To date no studies have been performed to investigate whether there are variations in the genomic or proteomic profiles in tumours from lung cancer patients around the world. Prospective studies would be required to examine if such biological differences indeed exist, and whether or not they could be a contributory factor to the inferior survival in Scotland.

iii) Stage at presentation

Table 2.2 demonstrates that the proportion of patients presenting with metastatic lung cancer varies from 28 to 45% around the world. Though undoubtedly some of this variation will be real, some will be due to the varying number of investigations performed; the more

investigations performed the more likely it is that metastases are found. As a result, the more recent publications will generally report higher rates of metastatic disease.

The allocation of cancer stage in every-day clinical practice is difficult and often judgments have to be made on relatively few investigations. Consequently, the accuracy of staging in population-based series will be far less robust than is observed, for example, in clinical trials where multiple investigations are performed to ensure accurate staging. Although when ever possible the more precise TNM staging was used wherever possible in this thesis, for many patients, particularly in the 1995 cohorts, these data were not available and therefore the alternate system of local, regional and distant stage was used. However, this latter system is very open to interpretation, for example in the classification of intra-pulmonary lymph nodes. In the TNM staging involvement of these lymph nodes indicates N1 or Stage II, but in the SEER system the disease is classified as 'Localised'. Some inconsistencies were also present in the previously collected Scottish 1995 data between pathological TNM staging and the 'local, regional, metastatic' system. This required amendment to ensure a consistent approach between the BC and Scottish cohorts. The patients in the 2002 and 2004 SCAN cohorts were mainly allocated a TNM stage at the multidisciplinary meeting by lung cancer oncologists and therefore staging would have been much more accurate.

In 1995 in Scotland, 31% of patients presented with distant disease compared with 37% in BC, but in 2002 in South East Scotland 42% had metastases at presentation. It seems unlikely that patients presented with more advanced disease so this is probably an artefact due to i) higher case ascertainment (92% 1995 v 96% in 2002), and ii) increased use of CT scanning and improved image quality. In 2004, the proportion of stage IV patients in South

East Scotland was 41%, suggesting that 40% is a more accurate estimate for Scotland, than the 1995 figure of 31%.

In 2002 35% of patients presented with regional disease, 14% localised and 9% unknown and in 2004 38% had regional disease, 12% localised and 9% unknown stage.

In recent publications reporting 'whole-population' data from the USA [33, 127], around 21-22% patients presented with localised, 26% regional, and 41-43% with distant disease. These figures are similar to those observed in the BC cohort. Therefore, though the proportion of patients presenting with metastases in Scotland was possibly similar to that in North America, there appears to be fewer patients presenting with localised disease; the stage that is most amenable to curative therapy.

In order to have long-term survivors, it is important that as many patients as possible receive potentially curative therapy; the higher the proportion of patients with early stage disease, the better the population-base outcome. For example, with a five-year survival rate of around 50% after surgery, a population with 15% surgical candidates will have a five-year survival rate of 2.5% less than a population with 20% of patients suitable for this treatment. Therefore, strategies are required to optimise the number of patients presenting with early stage disease.

The whole premise of cancer screening, and healthcare policy to reduce waiting times, is driven by the belief that earlier detection will automatically result in improved survival.

However, it is important to determine whether there are data to support this supposition, or whether the biological behaviour of the tumour is the primary determinant of outcome.

Currently, in the absence of an effective screening test, the majority of lung cancer patients are diagnosed with symptomatic disease. If the interval from symptoms to diagnosis has an impact on stage at presentation, then patients need to be aware of the potential significance of any new symptoms[182]. They then have to have access to medical practitioners who recognise the significance of these symptoms and instigate further investigations. However in lung cancer patients, the higher rates of co-morbid disease may disguise cancer symptoms, for example, a chronic cough from chronic obstructive pulmonary disease [128]. In a series of in-depth interviews with twenty-two patients recently diagnosed with lung cancer, Corner *et al* noted that patients frequently tried to manage their own symptoms, often not recognising them as serious and warranting medical attention. Patients often only presented to their GP when it reached a severity with which they could no longer cope [42, 43]. Only haemoptysis prompted an early visit to the doctor. Overall, a general decline in health had occurred over a median period of seven months prior to diagnosis, with the presenting symptom only present for a median of two months. There was no difference in the nature of the symptoms in patients who presented with operable disease, and in those patients who did not.

Table 8.1 shows the studies, written in English, published between 1990 and September 2006, which examined the impact of delays in presentation, diagnosis and treatment for lung cancer patients (search strategy: Pubmed using terms 'lung cancer' and 'delay', all reference lists searched to identified missed publications). The median time from first symptom to

treatment ranged from 70 to 112 days, and from presentation to a doctor, to commencing treatment, it was 48 to 109 days.

A number of the studies also examined the impact of delays on stage at presentation and/or survival. In an analysis of a database of a large Italian hospital, Bucherri and colleagues noted that although the survival of patients whose symptoms had been present for more than two months appeared to be inferior, on multivariate analysis only the presence of dyspnoea, chest pain or systemic symptoms were associated with increased hazard of death. Whereas, asymptomatic patients had a reduced hazard of death (0.76 (0.62-0.94)) [30]. In a study from the Hospital del Mar, Barcelona including 566 lung cancer patients, the interaction between first symptoms and diagnosis (SDI) for patients with lung tumours was complex; patients with a very short, or very long SDI, had a reduced hazard of death compared to those with a medium SDI [119].

Only one small surgical series of 172 patients demonstrated a negative impact of delays; fewer patients presented with operable disease when the delay was longer [39].However, eight other studies have either found no impact, or that those patients with a *longer* delay have an *improved* outcome. This is likely to be because patients with rapidly progressive symptoms have biologically more aggressive tumours and therefore present with more advanced disease.

A similar result has been noted in South East Scotland. In 2005, 539 patients were referred to the three hospitals in Lothian healthboard. The median survival for the 336 patients treated in under 62 days was 51 months (3.9-6.2) compared with 21.4 (24.4-28.3) for the 150

patients with a delay of more than 62 days (remaining 53 date referral unknown). The hazard of death adjusted for age, gender, performance status, deprivation, stage and pathology was 1.9 (1.4-2.6) for those treated after 62 days compared with those treated more quickly (Fergusson and Erridge unpublished data).

Consequently, although delays in diagnosis undoubtedly cause psychological distress to patients and their carers, it appears that for patients with symptomatic lung cancer, it is the biological behaviour of the tumour and not delays in presentation which is likely to be the main determinant of survival.

Over the last thirty years a number of lung cancer screening trials have been conducted to investigate the use of chest radiographs, sputum cytology, and latterly spiral CT scanning and biological markers. At present none of these have been proven to reduce mortality rates. Advocates of screening assert that the discovery of small lesions must improve outcome by detecting the lesion at a time when surgery is possible [89]. In the large US CT screening trial, 90% of patients with tumours <15mm had no evidence of nodal or distant metastases compared with 55% for tumours >36mm [91]. The estimated ten year overall survival of the 412 Stage I tumours which underwent resection was 88%, which the authors concluded was superior to SEER data [90].

However, screening may cause an apparent improvement in five-year survival rates by:

i) detecting tumours earlier, but not impacting on time of death (lead time bias)

ii) detecting lesions that would not have become clinically apparent during the patient's lifetime (over diagnosis) [148].

Until there has been a demonstrable reduction in mortality, the positive impact of screening for lung cancer cannot be confirmed [124].

In conclusion, there appeared to be a higher proportion of patients in Scotland presenting with regional stage disease. Therefore less patients were suitable for surgery, and consequently there were fewer long term survivors. Based on current evidence it does not appear that patient education on symptoms would result in an earlier diagnosis and the benefits of screening remains unproven.

Table 8.1 Publications in English 1990-2006 on delays in diagnosis and treatment of lung cancer and potential impact on survival

Author	Cohort	Median time symptom to doctor	Median time referral to diagnosis	Median time symptom to treatment	Outcome	Comment
Porta 1991 [152] Maguire 1994 [119]	Barcelona Spain referrals to hospital 1978-92 (n-566) Prospective database	-	60 days (symptom to diagnosis (SDI)) – same for all stages	-	Complex association of SDI and survival with patients with very short and very long SDI having reduced hazard death	No association between duration of symptoms and stage
Jones 1992 [105]	Devon GP practices 1986-90 (n=59) Prospective	-	31 days (0-713) GP to hospital	70 days (12-868)	-	-
Biling 1996 [18]	Cambridge referred for surgery only 1993 (n=37) Retrospective	-	Mean 32 days (21-42) GP to referral	Mean 109 GP to surgery	-	-
Dische 1996 [53]	UK patients receiving RT over a 3 month period 1993-4	21 days (CI 14-49)	7days (CI 0-63)	133 days (84-231)	-	Centres recruiting to CHART trials
Christensen 1997 [39]	Denmark referred to surgical unit 1994-5 (n=172) Retrospective	-	-	152 days if operable 182 days inoperable (Mann Witney U p=0.04)	-	Confidence intervals overlap. Asymptomatic patients more likely to be operable
Ringback 1999 [164]	Denmark referred to hospital (n=467)	-	Mean 43 days	-	No impact of delay from referral to surgery	-
Bozcuk 2001 [22]	Norfolk referral to a hospital 1998 (n-189) Retrospective	-	11days GP to hospital	48 days (GP to treatment)	No impact of hospital delay on survival	Small group so difficult to interpret
Aragonese 2002 [7]	Spanish Surgical Database1993-97 (n=1082)	-	-	35 days (1-154) diagnosis to surgery	No impact of delay on survival	No association with delay and stage

Ozlu 2002 [146]	Turkey referred to two hospitals 1992-99 (n=226) Retrospective	30days (2-365)	8 days (1-210) GP to diagnosis	71.5days (3-429)	-	No difference between pathological types
Koyi 2002 [107]	Sweden referred to chest unit 1997-98 (n=134) Prospective	21 days (0-256)	33 days (0-720) GP to hospital	189days (20-794)	-	No correlation of delays with stage
Quarterman 2003 [155]	San Francisco referred for surgery 1989-99 (n=84) Retrospective	-		92 days (2-641) detection to surgery	No impact of delay of surgery on survival	
Bucherri 2004 [30]	Italy referred to hospital (n=1277 with pathology)	12% asymptomatic 60days if symptoms			Median survival 43weeks if < 2mo and 32 if >2mo	But on multivariate hazard of death not significantly different
Allgar & Neal 2005[5, 142]	UK NHS register 1999 (n=2669)			38 days(mean 89 days) symptom to diagnosis		No impact deprivation, gender, martial status
Comber 2005[41]	EIRE Cancer Registry 1999	-	-	54 days (28-100 inter-quartile range) GP to treatment	Decreased hazard of death for all waits > 1 month	Decreased wait for treatment with more advanced disease
Corner 2005 [42]	Southampton detailed symptom mapping of 22 patients	45 days (0-330)	60 days (15-240) presentation to diagnosis	-	-	No impact of delays on operability
Myrdal 2005 [140]	Sweden identified by registry 1995-99 (n=466) Retrospective	-	-	140 days (102 days for Stage IV patients)	symptom to treatment <3/12 11% 3yr OS v >6/12 35%	Similarly longer hospital delay associated with better survival
Liberman 2006 [115]	Montreal referrals for surgery 1993-2002 (n=256) Retrospective	-	-	109 days (presentation to surgery)	-	No difference on pathological stage and delay Median time on waiting list 82 days
Loh 2006 [117]	Malaysia referrals to 2 hospitals (n=122) Retrospective		60 days symptom to hospital	33days hospital to treatment	No difference in survival for either delay	
Salomaa 2006 [166]	Finland referral to hospital 2001 (n=132) Retrospective	14 days	98 days (symptom to diagnosis)	112 days	Longer delay reduced hazard of death	No association between stage and delay

2) Patient related factors

i) Gender

In almost all population-based lung cancer series women have longer survival than men. The reasons for this and whether or not women truly are at greater risk for developing lung cancer than men, has been the subject of much debate [147].

Women may be more susceptible to lung cancer for two reasons. Firstly, due to different polymorphisms of the enzymes that help break down the carcinogenic polycyclic aromatic hydrocarbons in smoke (CYPIA1 [135] and GSTM1 [193]). Secondly, differences in the genes that control the re-proliferation of bronchial epithelium following damage (GRPR)[178]. However, categorical proof that women are at greater risk is difficult to establish as it is impossible to account completely for other variables such as, type of cigarette and duration of smoking.

The impact of oestrogen on lung cancer has also been heavily investigated. Case-control studies have demonstrated that hormone replacement therapy appears to *decrease* the risk of lung cancer, particularly in female smokers [59, 108, 169].

The improved population-based survival for women [72, 127] is particularly marked following surgery. In the Norwegian surgical series, the five-year relative survival was 56% for women, compared with 41% for men [188]. A similar result has also been observed in an American cohort of patients [10]. These studies could reflect lower rates of co-morbid disease in women, particularly cardio-vascular disease [203], or possibly different tumour behaviour.

Relative survival should adjust for the difference in life-expectancy between the sexes, but higher rates of smoking-related diseases in lung cancer patients compared to the normal population may make this adjustment inadequate [102]. The relative survival model of the combined 1995 populations demonstrated that women had a reduced hazard of death (HR 0.93-0.96). In British Columbia, the improved survival in women was most marked for patients undergoing surgery (median survival 37months men v 49 months women, log rank p=0.02), but the adjusted hazard of death was non-significant (HR 0.8 (0.6-1.05). In Scotland, the adjusted hazard of death for women was 0.9 (0.8-0.96) compared to men, but there was not a difference following surgery. Although this may simply reflect a smaller proportion of patients having this treatment; when the whole group receiving 'potentially curative therapy' was examined the hazard ratio of death was 0.81 (0.7-0.99) for women.

If a lung cancer population has a higher proportion of women the difference in survival might contribute to the improved survival. However, this was not the case in Canada and Scotland where around 40% of patients were women in both populations (χ^2 p=0.12).

ii) Age

The age profile of a population will impact on the observed overall survival. As was observed in the 1995 and 2002 comparison, the median age of lung cancer patients in Scotland is increasing. This is because the birth-cohorts from the 1920s to 1940s, with the highest risk of lung cancer, make up the bulk of the current patients. This trend will continue over the next decade, which might result in inferior lung cancer survival rates despite the use of more treatment. The data presented in Table 2.2 demonstrates that the median age of

patients diagnosed in late 1980s to early 1990s was between 60 and 65, whereas in more recent case-series the median age was 65 to 70 years.

A population with a large number of younger patients will always have better survival as i) the patients will be more suitable for aggressive curative therapies, and ii) patients are less likely to succumb to other causes of death..

The age profiles of the two 1995 populations were similar with median age of 70 years in both the BC and Scottish patients, although BC had a slightly higher proportion of patients under the age of 60 years (figure 5.1). The relative survival models (Table 5.9) demonstrated that the hazard of death in Scotland was still markedly increased even when differences in the age profiles were taken into account

iii) Performance status and weight loss

Performance status, or the ability to function in everyday tasks, is a strong predictor of survival following a diagnosis of lung cancer. However, there are little published data population-based data on performance status in lung cancer patients. In neither of the 1995 cohorts were these data collected, but in 2002 in South East Scotland 41% of patients had a PFS 0-1, 22% PFS2, 24% 3-4, and it was not recorded for 13% of patients. The median survival was 10.1 months, 4.5 months, 1.7 months and 2.6 months, respectively. In a population-based cohort of 309 patients diagnosed in BC in May and June 2002, 90% had a PFS 0-2 recorded by their GP, with a median survival of 14.7 months for those with PFS 0, 7.8 months if PFS 1, 5.7 months PFS 2 and 2.1 months PFS 3-4 (unpublished data Tyldesley, Roques and Erridge). De Rijke and colleagues report data from the Netherlands with 64% of

patients having a PFS 0-1, 19% PFS 2, 12% PFS3-4 and 5% unknown. However this paper does not report survival data.

Weight loss is also associated with a worse outcome, primarily as it is a predictor of more advanced stage disease. In a hospital based series Tammemagi *et al* showed that 40% of patients with Stage I disease had weight loss compared with 20% with Stage IV disease [192].

iv) Ethnicity/Race

Several series from the USA have demonstrated lower survival in black patients with lung cancer when compared with white patients. This appeared to be due to more black patients presenting with advanced disease [74], and lower use of lower use of surgery [10].

In Scotland only 4% of the population are of non-British or Irish origin (2001 census) compared with BC where 42% (of single ethnic group responses) are of British origin, 28% from other European countries, 19% Asian and 5% First Nations and the remaining 4% from other ethnic groups (1996 census).

Unfortunately data on ethnic origin was not collected in either country in 1995 and therefore the impact of race could not be examined in this thesis.

v) Social deprivation

As has been alluded to earlier, social deprivation has in some studies been shown to have an impact on both use of treatment and survival in lung cancer patients [209]. Social deprivation can either result in inferior access to healthcare [23, 33, 78, 127], less treatment delivered

[10], or increased rate of death from co-morbid disease [128]. The lower use of treatment may be a result of higher levels of co-morbid disease [128], but does not appear to be due to more advanced disease at presentation [27, 173].

For the BC patients only the data on household income were available. It should be noted that the use of post-code to determine median income is a crude estimate of the social deprivation of any particular individual [21, 118]. However, it appears that patients who resided in wealthy areas with a household income of $CDN60000 or more per annum were more likely to undergo surgery or chemotherapy, but use of radiotherapy was not increased. The overall survival was not affected by income.

In Scotland, data on a broader range of factors (overcrowding, male unemployment, social class and car ownership) are used to estimate deprivation and have been shown to be superior to using income alone. The group of patients living in more deprived areas were less likely to undergo surgery (radiotherapy and chemotherapy not statistically different), and the survival was inferior (median 3.5 v 4.0months).

The apparently higher proportion of patients living in a deprived area in Scotland may be an artifact due to the different methods of defining deprivation between the two countries. In Scotland, Carstairs' index groups 4 to 7 represent around 58 % of the population of Scotland, whereas for BC the median household income was used to split the population into two groups. Also how comparable these measures are of true deprivation is unknown.

Both Canada and Scotland have state-run healthcare systems which endeavour to offer equitable access to healthcare for all citizens. A number of American and Canadian comparisons [11, 21, 78] have demonstrated that impoverished patients fared better in the Canadian healthcare system than in the USA. Why Scots do not similarly benefit from state-run health care is unknown, but could reflect increased co-morbidity in people living in deprived areas [128], which make treatment more difficult to deliver and results in deaths from other causes. Though the impact of deprivation was less marked than for other factors, the adjusted hazard of cause-specific death in the less deprived areas was 0.9 (0.85-0.99 p=0.03) compared with the more deprived areas, whereas the other significant factors such as age, stage, no pathology and region all had p values </= 0.01.

In summary, the possible increased social deprivation in Scotland could be a contributory factor to the inferior survival of Scottish patients, but this effect is likely to be minor in comparison to other factors.

vi) Life-style

a) Smoking

Unfortunately data on smoking was not reliably recorded in any of the three cohorts, but smoking is obviously the primary life-style factor that could potentially impact on the survival of lung cancer patients. Not only is smoking the prime aetiological factor, accounting for 90-95% of lung cancers, it is also the main causative agent for many of the co-morbid diseases (COPD, cardiovascular, peripheral vascular and cerebrovascular disease).

In a recent analysis of the Eindhoven Cancer Registry more than half the lung cancer patients between the ages of 50 and 64 years had one or more serious co-morbidity, compared with around a third of patients with colorectal, prostate, breast and lymphoma in the same age group [203]. This difference was particularly marked for COPD, which was present in around 20% of the lung cancer patients, and 5%of patients with other malignant diagnoses. The rates of co-morbidity increased with age, with 72% of men and 61% of women over the age of 80 years having at least one serious co-morbid disease. These high levels of co-morbid diseases will impact on overall survival.

For more than 25 years, researchers from the University of Glasgow have been following a large prospective cohort of residents in two regions of Strathclyde (Renfrew and Paisley) examining a range of public health issues. In a recent publication they noted a positive correlation between high levels of carboxyhaemoglobin (a biochemical marker for level of smoking) and deaths from lung cancer, cardiovascular, cerebrovascular disease and COPD [88].

In Scotland currently around 30% of Scots smoke, compared with 16% of British Columbians. This lower rate of smoking will result in less co-morbid disease and could therefore explain some of the difference in survival observed between the two cohorts.

b) Diet

A number of prospective cohort studies have demonstrated that a diet rich in fruit and vegetables may mitigate some of the risk associated with smoking [168, 180], and improve the prognosis of lung cancer patients [181]. The diet in Scotland is notorious for being low in

fruit and vegetables. In 1996, only 18% of people in Scotland ate five portions of these foods each day (13% in the most deprived group), and only 19% knew of the recommended guidelines. Fortunately the health education message appears to be hitting home, and in 2004 33% ate five portions a day and 63% knew of the recommendations, although only 49% came from the most deprived group [123].

The population of British Columbia is almost all immigrants who have moved there from all over the world during the last 150 years. Though citizens with British ethnic origin constitute a sizeable minority, many come from the Mediterranean area, Balkan states, Indian subcontinent, and South East Asia. This has resulted in one of the healthiest and varied diets in the world, with low consumption of fast-foods. In addition, a high proportion of the population also take regular exercise. For the period 1995-7 the age-standardised mortality rate for ischaemic heart disease was 113 per 100,000 for BC [66] compared with 158 per 100,000 in Scotland in 1996 [174]. This clearly demonstrates that the lower smoking rates, healthier lifestyle and different ethnic mix in BC may have improved the outcome of lung cancer patients.

In conclusion, the life-style of Scottish patients with higher rates of smoking and a diet with less fruit and vegetables may be a contributory factor to the inferior survival when compared with BC.

3) Use of treatment

i) Surgery

In lung cancer the proportion of individuals undergoing surgery is the strongest determinant of the five-year survival rate of a population. With good patient selection, around 40-50% should be alive five years after this treatment, compared with 15%, after conventionally fractionated radical radiotherapy. Due to the different methods of reporting the data (whole population v pathological subtypes) it is difficult to give exact figures to demonstrate the correlation between surgical rate and survival, However, in populations where more than 20% of patients undergo resection (SEER series [72, 160], Bas Rhin, France (NSCLC only) [68], Victoria, Australia [163]) the observed five-year survival rates exceed 10%, whereas in populations with a resection rate of around 10% (Ireland [120], Yorkshire [37]) the five-year survival rates are below 10%. In BC, 21.1% of the population underwent a resection (29.2% NSCLC) and the five-year relative survival rate was 12%, compared with 10.6% of Scottish patients undergoing surgery (18.2% NSCLC), with an overall five-year relative-survival rate of 6%.

In both BC and Scotland in 1995, age and social deprivation were associated with reduced odds of having surgery, but in 2002 in South East Scotland advanced age was the only patient-related factor associated with lower use of surgery. In the seven years between 1995 and 2002 there was no increase in the use of surgery in South East Scotland; the rate in 1995 was 10.2% and in 2002 was 10.5% (though the median age of the population increased from 70 to 72.5years). However, the optimal treatment model (Table 7.4) suggested that this was due to, i) only 23% of patients presenting with Stage I-II disease, ii) a high proportion have

severe COPD, and iii) many had a poor performance status, only between 10.4 and 11.8% of patients from South East Scotland appear to be suitable for surgery.

Therefore, it may be that unless more patients present with early stage disease and co-morbid diseases can be managed more successfully, the surgical rate in Scotland may have reached a plateau. Without this change survival rates could only be improved by increasing the proportion of patients receiving radical radiotherapy.

Of the patients who underwent a resection in BC, 2.7% died within a month of surgery (post-operative death) compared with 9.2% in Scotland (but lower in South East Scotland (3% in 1995 and 2% 2002)). The 1995 Scottish surgical mortality was much higher than most surgical series published in the last twenty years.

In a population-based series of 132 patients operated in Western Australia, 6% died of post-operative complications (3% lobectomy and 12% pneumonectomy), and another 47% had a serious, but non-fatal complications (primarily infection or persistent air leak)[134].

In a random sample of 2118 patients over the age of 65 from the SEER database operated on between 1986 and 1996, the 30 day mortality rate was 6% for patients in hospitals which operated on less than eight patients per year. This was compared with 3% in centres which operated on more than 66 patients per annum [9]. There was also an impact on overall survival; with a five-year survival rate of 33% in the smaller hospitals and 44% in the larger. After adjustment for other factors, such as age, gender, stages of cancer, operation, income, and co-morbid disease the odds of death from lung cancer by five years was 0.8 in the larger hospitals when compared with the smaller hospitals.

In a Spanish series of 2994 cases operated on between 1993-7 around 7% of patients died within 30 days of their operation. Factors which were associated with increased risk of death were older age, poor performance status, incomplete resection, exploratory thorocotomy, and peripheral vascular disease. There was no effect of hospital size on the post-operative mortality rate [69].

In the large Norwegian series of 3211 patients operated on 1993-6, the 30 day mortality was 4.8%, but there was no impact on the five-year survival rate, of the number of patients operated on each year in each hospital [188].

The reason for the lack of impact of hospital size on patient outcome in the Norwegian and Spanish patients may either be because these patients were operated on more recently and information on best practice had, by then, filtered down to smaller centres, or the public healthcare system in the European countries ensures better equity of quality standards. No impact of case-load could be seen in the Canadian patients.

It therefore appears that the post-operative mortality rate in BC was lower than most reported series, but in Scotland it was higher.The cause of the higher post-operative mortality in Scotland is unknown. There was no statistical association with social deprivation, but the mortality rate varied markedly between regions; 14% in Region 1, 5% in Region 3 and 3% in Region 2 (Chi squared $p=0.002$). This could in part be explained by the fact there were fewer pneumonectomies performed in Region 2 (34%), compared with Region 1 (40%) and Region 3 (44%), but the mortality following pneumonectomy in Region 2 (6%) was under half that observed in Region 1 (19.5%).

The higher rate of post-operative deaths contributed to the inferior survival in Scotland but on multivariate analysis of patients surviving more than one month following survival still demonstrated an increased hazard of death for Scots.

Table 8.1 shows the five-year survival rates in a number recently published surgical series. The effect of stage at presentation on survival, is clearly demonstrated. In the Japanese series other factors that were associated with improved survival included female gender, younger age and adenocarcinoma [79].

In a subgroup of Stage IA resected cases of the large SEER series, improved survival was noted in patients under the age of 70 years, with well differentiated tumours, lesions less than 10mm in size and bronchoalveolar pathological subtype [158]. In the BC and Scottish series bronchoalveolar carcinomas were included within the adenocarcinoma group, but an analysis of the survival of the patients from BC (where separate data were available) did not demonstrate a difference in survival following surgery between bronchoalveolar and adenocarcinoma (median survival 63 v 59 months).

The overall survival rate in Scotland was around 50% at five years of patients with stage I disease, and 30% with Stage II disease, which was not dissimilar to the rates seen in Norway and Australia. Though the SEER results appear superior, the series report *cause-specific* not *overall survival*, and the data from Japan may be biased as it is based on retrospective questionnaires reported by surgeons. However, the survival for the stage III resected patients in Scotland does appear to be inferior at 8% compared with 15-30% in most other series.

The reasons for this area uncertain but may be due to under-detection of metastases (real stage IV not stage III). Other explanations, such as different tumour behaviour, are speculative.

In conclusion, the use of surgery in Scotland is lower than in many countries, but this may be appropriate as medically fit patients with early stage disease constitute a lower proportion of patients than in BC and reported in other series. The survival following surgery was worse in Scotland than BC, partly due to more post-operative deaths. However, compared to other series Scottish patients with early stage disease appear to have similar survival, but those with stage III disease fared less well.

Table 8.1 Outcome following surgery in population-based series

Author/Year	Population	Distribution of stage	Survival
Strand (2006)[188]	Norway 1993-6 3211 pts Norwegian Cancer Registry	65% Stage I 23% Stage II 10% Stage III 2% Stage IV	five-year RSR 46.4% 58% (50% OS) Stage I, 28 %(25%) Stage II 18% (16%) Stage III
Freixinet (2006)[69]	Spain 1993-7 2994 pts reported to **surgical register**	49% Stage I 17% stage II 34% Stage III	five-year OS ~38%
Goya (2005)[79]	Japan 1994 **retrospective audit of surgical cases**	52% Stage I 15% Stage II 20% Stage III 3% Stage IV	five-year OS IA 80%, IB 60%, IIA 60%, IIB 42%, IIIA 30%, IIIB 19% IV 20%,
Bach (2001)[9]	SEER random sample of 2118 patients >65yrs operated 1986-96	69% Stage I 20% Stage II 11% Stage III	five-year OS 38%
Radvin (2006)[158]	SEER 1988-97 17,310 patients	68% Stage I 22% Stage II 10% Stage III	five-year **CS** IA 77%, IB 62%, IIA 49%, IIB 36%, IIIA 36-23%
Mina (2004)[134]	Western Australia Cancer Registry 1996 132 patients	57% Stage I 15% Stage II 28% Stage III	five-year OS 51% Stage I, 45% Stage II 15% Stage IIIA
BC 1995- this study	438	54% Stage I 19% Stage II 13% Stage III 2% Stage IV 12% unknown/SCLC	Five-year OS 38.6% 48% Stage I, 27% Stage II 17% Stage III
Scotland 1995 - this study	406	40% Stage I 22% Stage II 12% Stage III 1% Stage IV 25% unknown/SCLC	Five-year OS 35.9% 52% Stage I, 29% Stage II 8% Stage III

ii) Radiotherapy

Radiotherapy is the most frequently used treatment modality in lung cancer. In BC, 40.3% received radiotherapy compared with 36.5% in Scotland (Chi-squared p=0.004), though the adjusted odds ratio was 0.9(0.8-1.04).

In either country, very few patients received radical radiotherapy (2.2% in BC and 2.5% in Scotland), though more patients received adjuvant thoracic radiotherapy for L-SCLC in BC (57% in BC v. 14% in Scotland). The fractionation schedules used were fairly similar reflecting the fact that many of the BC Radiation Oncologists were trained in the UK.

In BC, radiotherapy was more frequently used in younger patients, those with regional or metastatic disease, or with a tissue diagnosis. In addition, patients living *closer* to a cancer centre were more likely to receive radiotherapy, whereas in Scotland those living *further* from a cancer centre were more likely to receive radiotherapy. The other factors, including younger age and more advanced stage disease were also important in Scotland, but patients with SCLC were less likely to receive radiotherapy than those with NSCLC. The reason for the increased use of radiotherapy in Scots who had further to travel is unknown, but in the mid 1990s in Glasgow (where the majority of the patients with short travelling times resided) the cancer centre had particularly long waits of more than six weeks for radiotherapy and this may have influenced treatment recommendations. Barbera and colleagues observed a similar effect in Ontario in the lung cancer patients treated between 1994-1996 when radiographer shortages resulted in long waits for treatment [12].

.

The use of radiotherapy in BC and Scotland, was similar to that reported in most other series that included patients without pathological confirmation [37, 48, 120, 163], though was a little lower than was observed in New South Wales, where 56% of patients received radiotherapy [201]. In the large SEER series of patients diagnosed 1975-1999 (all of whom had pathological confirmation), 51% of men underwent radiotherapy and 47% of women [72]. In BC 43.8% of pathologically confirmed cases received radiotherapy, whereas in Scotland this was a little lower at 40.3%.

The Scottish model described in chapter 7 (Table 7.5) estimated that 66% of patients could benefit from radiotherapy as part of initial therapy. In Canada, Tyldesley *et al* estimated that 44.6% of patients (+/-3.6%) would need radiotherapy during the initial treatment and 16.5% (+/-1.5%) later (lifetime use of 61%)[197]. The Australian model estimated that 76% of patients would require radiotherapy during the course of their illness [49].

Obviously the optimal rate of use of radiotherapy will vary between countries according to the distribution of the stage of presentation, pathological subtypes and differences in patient's suitability for treatment. In addition, the indications for radiotherapy differ, either because of new data (Canadian model was produced in the late 1990s) or different interpretation of the evidence. For example, in the Canadian model radiotherapy was only administered to patients with L-SCLC who were responding to chemotherapy. Evidence now suggests that thoracic radiotherapy should be given as early as possible with chemotherapy before the response can be assessed [61]. Also, in the Canadian model, radiotherapy was only given to patients with E-SCLC if they failed to achieve a complete

response to chemotherapy. However, if such an approach was adopted in the Scottish model the optimal radiotherapy rate would only change by 1% as it is the first three decision steps (pathological type, stage distribution and performance status) that have the most impact.

The rates observed in BC and Scotland were lower than the models predicted, but discussed in chapter 7, one of the main unknown factors is the severity of the thoracic symptoms and whether or not they require palliation with radiotherapy. The decline in use of palliative radiotherapy over the period 1995 to 2004 (see appendix 3) has been matched with an increase in the use of chemotherapy. This suggests that clinicians are opting for the latter treatment, which has been demonstrated to improve median survival and one-year survival rates in patients with metastatic disease, unlike low-dose palliative radiotherapy [44].

An alternative, benchmarking approach was adopted by the team from Kingston, Ontario. This technique assumes that areas with no resource restrictions and no fee incentives should have optimal use of radiotherapy. In the regions that they felt met the above criteria, the use of radiotherapy was 41.3% (49.3% NSCLC and 47% SCLC), but the rate varied from 23% to 43% in Canada, to over 60% in some SEER regions. The lower rate of use in Canada correlated with longer waiting times for radiotherapy [12]. This approach, developed by the business community, is useful but it is not possible to ensure, even with Ontario's practice guidelines and multi-disciplinary working, that every patient who might have benefited from radiotherapy was discussed with such a lung cancer specialist.

Although the rate of use of radiotherapy in South-East Scotland did not increase over the period 1995 to 2002, the trebling of the use of radical radiotherapy over this period is probably the reason for the improvement in overall survival. This demonstrates the importance of multi-disciplinary discussion to ensure that all patients who could benefit from this treatment are seen by a specialist radiation oncologist.

It appears that in South East Scotland, the rate of surgery may have reached a plateau, but if the use of radical radiotherapy was that predicted by the model the number of long term survivors could potentially be increased. Around a 15-20% patients are alive five years after both radical radiotherapy for NSCLC and chemo-radiation for L-SCLC[113], therefore an increase in the use of high dose radiotherapy from 3.7%(1995 actual) to 24.7% (model optimal) would increase the five year survival rate by around 3.1-4.2%. Though this appears a tiny increase, it represents more than 50% increase in the number of patients alive at five years. Whether or not this could be realistically achieved, particularly in light of the ageing lung cancer population, is unknown.

In conclusion, the overall use of radiotherapy was lower in Scotland than BC, but this could be accounted for by differences in patient and tumour characteristics. The use of radical radiotherapy in 1995 was low in both countries, but fewer Scots received potentially curative chemoradiation for L-SCLC which might have affected the number of long term survivors. The use fo radiotherapy in both countries was lower than models of optimal use predict and increased use of radical radiotherapy might improve five-year survival rates

iii) Chemotherapy

Until recently the majority of chemotherapy was delivered with palliative intent. Only a few patients with L-SCLC can be cured by chemotherapy alone, with around 5% alive at five years, but when combined with thoracic and cranial radiotherapy the cure rate increases to around 15-20% [76].

Recently, data has been published which demonstrated that the delivery of post-operative chemotherapy can improve the five-year overall survival rate of patients with pathological Stage II and III NSCLC by around 5% [56, 207]. However, the impact of chemotherapy on long term lung cancer survival is minimal; patients with L-SCLC represent 6% and those with resected Stage II and III NSCLC 5% of all lung cancer patients. In addition, within each group only a minority of patients actually benefit and therefore at five years only around 1.5% of all lung cancer patients are alive due to the use of chemotherapy.

The majority of lung cancer chemotherapy is given to prolong survival and palliate symptoms. For patients with extensive SCLC the survival is increased from a few weeks to several months with the use of chemotherapy, but the improvement is less marked for NSCLC with the median survival increasing by around two months[44]. However, though the improvement in median survival is small the number of patient alive at one year trebles from 5% to 15% [6].

Recent trials have compared a variety of combinations of newer chemotherapy agents, but to date no particular combination appears greatly superior to the others in terms of either

response or survival, though the toxicity profiles vary [171]. Newer biological agents have yet to have a major impact on survival in lung cancer with the majority of trials failing to show survival benefit. To date only erlotinib (an epidermal growth factor receptor inhibitor) has been demonstrated in Phase III randomized controlled trials to improve survival, and this effect was primarily observed in non-smokers with a good performance status [67, 176].

In 1995, the use of chemotherapy in SCLC in BC was 76% compared with 63% in Scotland (χ^2 $p<0.001$), though the use increased in South-East Scotland to 68% by 2002, and to 71% by 2004 (see Appendix 3).

In Ireland (1994-1998) 60% [120], The Netherlands (1990-1994) 73% [101], France (1993-94) 92% [114] and Australia (1993-96) 83% [201] of patients with SCLC received chemotherapy. In the USA, 69% of patients with SCLC on the National Cancer Database (NCD) who were diagnosed in 1995 (hospital registrations only) received chemotherapy [76]. Therefore the use of chemotherapy in SCLC in BC is comparable to most other series, but the use in Scotland, although improving, remains below most international series.

61% of patients with L-SCLC received chemoradiation in BC compared with 14% in Scotland. A number of trials were published in the late 1980s and early 1990s confirming the benefit to survival of adding thoracic radiotherapy in L-SCLC [104, 149]. BC was at the forefront of introducing this treatment, and was the lead centre for one of the main trials on the timing of thoracic radiotherapy [139] and therefore combined treatment was the standard of care even in 1990 [113]. The introduction of combined treatment appeared to have been delayed in Scotland.

The data demonstrating the survival benefit of chemotherapy for patients with metastatic NSCLC was published in 1995 [6] (although it had been presented at a meeting the previous year), and therefore its use in 1995 was much lower than was observed in more recent series. In 1995, in both BC and Scotland, 8% of patients with NSCLC received chemotherapy. This rate increased in South East Scotland to 12% in 2002, and 19% by 2004 (excluding post-operative adjuvant chemotherapy).

In Ireland (1994-1998) 13%, Netherlands (1997-1998) 13% [48], Australia 10% and France (1994-97) 39% (excluding post-operative) of NSCLC patients received chemotherapy.

In a group of patients in the USA over the age of 65 diagnosed between 1991 and 1996 with stage IV NSCLC, 26% received chemotherapy [57], and in a second series, also using SEER data, which included patients over 65 years with Stage IIIB and IV NSCLC 31% received chemotherapy. As data on the use of chemotherapy is not collected by SEER (above studies used Medicare data) it is difficult to ascertain a true population-based use of chemotherapy in USA. In the National Cancer Database (hospital based register) 30% of all lung cancer patients received chemotherapy. Therefore, if around 85% of patients have NSCLC, approximately 23% of NSCLC patients received chemotherapy in 1995 (including some post-operative chemotherapy).

In summary, the use of chemotherapy in South East-Scotland is still below that in the USA, but exceeds most other world series from the mid to late 1990s.

In both BC and Scotland younger patents, those with SCLC or with more advanced disease were more likely to receive chemotherapy. However in BC, patients from an area with higher than average income were more likely to receive chemotherapy. This effect was not observed in Scotland. Why such an effect should be seen in BC but not Scotland is difficult to explain.

The use of chemotherapy has increased over the last decade, but without more detailed data on why patients are not offered or decline this treatment, it is impossible to know whether or not this can be increased further. The chemotherapy agents currently used to treat lung are difficult to deliver to patients with severe ischaemic heart disease (increased risk of myocardial infarction with platinum) and lung disease (gemcitabine pulmonary toxicity), and are all very myelosuppressive. Around 20% of patients receiving palliative chemotherapy for advanced NSCLC require acute hospital admission for toxic side-effects, such as neutropenic sepsis, nausea and vomiting, and renal failure[165].

In addition, many lung cancer patients who are offered chemotherapy decline it either based on prejudice against chemotherapy, or after being told of the possible benefits and side-effects[179]. Until more efficacious and less toxic agents are available it seems unlikely that the use of chemotherapy, particularly in advanced NSCLC, will increase in Scotland.

In conclusion, in 1995 the use of chemotherapy for NSCLC was low in both BC and Scotland, but fewer Scots than Canadians received chemotherapy for SCLC. However, this would only have a minor impact on long term survival rates.

Table 8.3 Summary of potential factors contributing to inferior survival in Scotland compared with BC

	Factor	Cause of inferior long term survival in Scotland
Tumour related	Pathology	No
	Biology	Possibly
	Stage	Probably
Patient related	Gender	No
	Age	No
	Ethnicity	Unknown
	Deprivation	Possibly
	Lifestyle	Probably
Treatment	Surgery	Yes – lower use + worse outcome
	Radiotherapy	Possibly – lower use in L-SCLC
	Chemotherapy	Unlikely

Conclusions and Future research

The aim of this thesis was to test the hypothesis that the outcome of lung cancer in Scotland is poor, and that this could be improved by optimal use of treatment.

It has been demonstrated that the survival of Scottish lung cancer patients is indeed inferior to that observed in British Columbia, and that this appeared to be due to a greater proportion of patients presenting with regional disease, less use of treatment (particularly surgery), and possibly other factors, such as life-style.

The primary determinant of population-based survival for lung cancer is the proportion of patients undergoing surgery, and to a lesser extent radical radiotherapy. Chemotherapy has only a minor impact on long term survival.

Although it may be possible for there to be a small, further increase the proportion of patients receiving radical radiotherapy, which would slightly increase the number of long term survivors, in order for the outcome in Scotland to similar to that in BC, the number undergoing surgery would have to double. It appears unlikely, based on the current distribution of stage and frequency of co-morbid diseases, that this could be achieved. The proportion of patients with COPD and ischaemic heart disease is unlikely to reduce over the next decade, as the average age of lung cancer patients will actually *increase*. In addition, in the absence of effective screening the proportion of patients with early stage disease is unlikely to change in the near future. In light of the lack of impact of diagnostic delays on lung

cancer survival it may be that tumour biology is the principal determinant of stage at presentation and outcome for patients with lung cancer.

In order to confirm or refute this prospective studies are required. It would therefore be informative to perform a prospective study in Lothian, Fife and Vancouver simultaneously examining the issues of delays in presentation and tumour biology. Such a study could also investigate the reasons for the poor life-expectancy of the Scottish population, such as life-style and co-morbid disease. By conducting this study prospectively, many factors that could not be addressed in the retrospective study, such as delays in diagnosis, accurate and complete recording of performance status, staging and co-morbid diseases could be assessed formally. In addition, the reasons behind management choices could be researched. By recording all these prognostic factors, along with all treatment delivered, and by tracking survival, it would then be possible to combine these data with studies of tumour genomics or proteomics to examine if there are different biological profiles of lung cancer in Scotland and BC.

Summary

The survival of lung cancer patients in Scotland does indeed appear to be inferior to that seen in British Columbia, but the reasons for this are more complex than simply under-use of treatment. Fewer patients in Scotland are actually suitable for surgery, and even if the use of radical radiotherapy were maximal, the survival will never match that in Canada. Other factors, such as, tumour stage at presentation, lifestyle, co-morbid diseases, and possibly tumor biology, appear also to be important.

Appendix 1 : BC questionnaires

Dear Doctor,

We are performing a study looking at the treatment and survival of all individuals diagnosed with lung cancer in British Columbia in 1995.

Your patient …….. date of birth …… date of death…… was recorded in the British Columbia Cancer Registry as being diagnosed with lung cancer. We would be very grateful if you could complete the following questionnaire.

Name _____

Date of Birth (mm/dd/yy) _____/ _____/ _____

Date of Death (mm/dd/yy) _____/ _____/ _____

Postal Code ___ ___ ___ ___ ___ ___

Was the diagnosis of lung cancer pathologically confirmed YES ____ NO _____?

If yes how

		Tick which
Bronchoscopy	biopsy	
	brushings/ washings	
Sputum cytology		
Fine needle aspirate	Primary	
	Lymph node	
	Other metastases	

If no how was diagnosis made?

	Tick all appropriate boxes
History and examination	
Chest X-ray	
CT scan of chest	
Autopsy	
Other please describe ……	

Was this patient referred to a lung cancer specialist (oncologist, respiratory physician, thoracic surgeon)?

YES ____ NO _____

If yes, to whom

_____

at _____ Hospital.

If no, why?

	Tick appropriate box.
Patient dying	
Patient refused	
Co-morbid disease–please describe _____ _____ _____	
Diagnosis made at autopsy	

If possible, we would like to try and establish the performance status of all the patients diagnosed with lung cancer. From your records is it possible to grade the person's daily activity?

YES _____ NO _____

Tick appropriate box

Performance status		
0	Fully active, able to carry out all their normal activities	
1	Restricted in strenuous activity but able to carry out light work e.g. house work, office work.	
2	Ambulatory but unable to carry out any work activities. Up and about >50% of the day.	
3	Capable of only limited self care confined to bed/chair >50% of the day	
4	Completely disabled. Cannot carry any self-care. Totally confined to bed/chair.	

Many thanks for your assistance in completing this questionnaire.

Appendix 2: South East Scotland 2002 study documentation

Dear Doctor,

Study – 'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

R.e _____ dob __/__ /___

_____

We are performing an audit of the management of all patients in Lothian, Borders and Fife diagnosed as having lung cancer in 2002, We will then compare this with a previous study performed in 1995. We shall be identifying all patients through the national cancer registration system, and have obtained permission from the Caldecott Guardians in the relevant NHS institutions to use patient identifiable data from this source for this purpose.

As far as possible we are obtaining treatment information collected from prospective audit through S E Scotland Cancer Network. In this case we are relying on the implied consent given by patients when they attend hospital to use of their data for clinical audit.

There are some patients recorded by Cancer Registration, however, about whose management we do not have any information. The above patient is recorded as being registered with your practice at the time of diagnosis and as still alive.

The Multi-Centre Research Ethics Committee for Scotland has approved this study, subject to obtaining the consent of any patients not directly under our care, who are still alive.

We would therefore ask if you would firstly ***check your records to ensure that the diagnosis of lung cancer in 2002 is correct*** *and then, assuming the diagnosis is valid,* approach this patient on behalf of the study group, to ask their consent to allow you to release this information to us. If the diagnosis appears to be incorrect, please let us know so that we can inform the cancer registry and they can amend their records. Any information which you release to us will be handled by audit staff trained in the requirements of data protection and working to approved methods of data handling. Whilst the unique identifiers are still present on the file, all data will be kept on the SCAN audit network, with full security. The data file prepared for analysis will be anonymised.

Therefore, assuming that your records indicate the diagnosis of lung cancer in 2002 to be correct, we would be grateful:

1. If the patient is still alive and you are in agreement, could you kindly forward to the patient the enclosed patient information sheet, consent form and envelope. Once the patient's consent has been returned to us, we will contact you again with the questionnaire for completion.
2. If the patient is alive but you do not feel is it appropriate for us to have this information, or the patient is no longer looked after by your practice we would be grateful if you could complete and return to us the form 'GP reply Version2'
3. If the patient has died could you kindly complete the enclosed questionnaire titled 'GP questionnaire patient Dead' and return it to us.
4.

We appreciate that this may involve you in some time and trouble, but we are anxious to ensure as complete as picture as possible about the outcomes for patients with this very unfortunate diagnosis.

If you have any questions or require further information please get in touch with me at the address above.

Many thanks for your assistance.

Yours sincerely

Dr Sara C. Erridge

on behalf of the SCAN Lung Cancer Group.

'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

Sara C. Erridge[1,2] Jamie-Megaw, Ron Fergusson[3], Allan Price[1,2], Janet Ironside[2], Felicity Little[2], William Walker[14], Anna Gregor [2,3] Jillian Campbell[5], Roger Black[5] *on behalf of the South-East Scotland Lung Cancer Network*

[1]University of Edinburgh, [2] Edinburgh Cancer Centre, [3] South East Scotland Cancer Network, [4]New Royal Infirmary Edinburgh,[5] Information Services, NHS National Services Scotland

Patient _____ dob ___/___/___

Address _____

_____

☐ I **do not** feel it is appropriate to approach my patient

_____ date of birth __/___/___ for this consent.

Name _____Signature _____Date ___/____/___

☐ This patient has passed away, date of death ____/ ____/____

(please complete enclosed questionnaire)

☐ This patient is no longer registered at this practice

New practice is Not known ☐

_____

_____

_____

☐ Cancer registration diagnosis was incorrect.

Final diagnosis was_____

GpreplyVersion3

Dear .....

I have been approached by the South East Scotland Cancer Network for information regarding your lung cancer. I cannot release this information to them without your permission.

If you are happy for this information to be released please return the signed consent form in the enclosed stamped addressed envelope.

Yours sincerely

Dr

GplettertopatientVersion1

Study – 'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

Patient Information sheet Version1.

We are performing a study to look at the treatment of lung cancer in South East Scotland and how it has changed over the last seven years. In 1995, a large Scottish National Audit of Lung cancer was performed and we would like to see how the treatment and outlook changed for patients, like yourself, who were diagnosed with lung cancer in 2002.

According to the Scottish Cancer Registry, you were recorded as being diagnosed with Lung Cancer in 2002. The Scottish Cancer Registry is a database run by NHS Scotland, which includes details of all patients diagnosed with cancer. It is used to increase our understanding of cancer in Scotland, how it is managed and to plan better services for cancer patients.

We are approaching patients to ask their permission to allow their General Practitioners to release information about their medical care to us. We will be asking your doctor about treatment you received. Any information will be handled in a confidential manner by specially trained audit staff working for the South East-Scotland Cancer Network.

If you are happy for your GP release this information to us, we would be very grateful if you would initial the box and sign and date the enclosed consent form and send it back to us in the stamped addressed envelope provided.

If you or your family would like further information on this study and/or the results we can be contracted at

SCAN Audit Office
Edinburgh Cancer Centre
Western General Hospital
Edinburgh
EH4 2XU

Patient Consent for Release of Information (Version2)

'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

Sara C. Erridge[1,2] Jamie Megaw[3], Ron Fergusson[3], Allan Price[1,2], Janet Ironside[2], Felicity Little[2], William Walker[14], Anna Gregor [2,3]
Jillian Campbell[5], Roger Black[5] *on behalf of the South-East Scotland Lung Cancer Network*
[1]University of Edinburgh, [2] Edinburgh Cancer Centre, [3] South East Scotland Cancer Network, [4]New Royal Infirmary Edinburgh,[5] Information Services, NHS National Services Scotland

☐ I have read 'Patient Information sheet Version 1'and **I agree** that my General Practitioner can release to the SCAN Lung Cancer Group information on the care I have received for my lung cancer.

☐ I understand that my permission is voluntary and that I am free to withdraw my permission at any time.

Name _____Signature _____Date ___/____/___

(Please initial the boxes and sign and date, and return to us in the enclosed stamped addressed envelope)

OR

☐ I have read the letter '**Patient Information sheet Version 1**'and **I do NOT agree** that my General Practitioner can release this information

Name _____Signature _____Date ___/____/___

(Please initial the boxes and sign and date, and return to us in the enclosed stamped addressed envelope)

Dear Doctor,

Study – 'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

Re.

You may remember we wrote to you previously requesting permission to approach your patient for their consent for release of information on their lung cancer care to us. They have now given us their consent, a copy of which is enclosed.

We would therefore be very grateful if from your records you could complete the attached questionnaire.

We appreciate that this may involve you in some time and trouble, but we are anxious to ensure as complete as picture as possible about the outcomes for patients with this very unfortunate diagnosis.

If you have any questions or require further information please get in touch with us at the address above.

Yours sincerely

Dr Sara C. Erridge
on behalf of SCAN Lung Cancer Group

Gpletterwithconsentversion1

'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

GP questionnaire patient ALIVE

Patients Name _____

Address _____

DOB ____/____/_____

Date cancer diagnosed ____/ _____/ _____

How was the diagnosis made?

Clinical	☐
CXR	☐
CT scan	☐
Bronchoscopy	☐
Other	_____

Was the cancer

Localised to the chest	☐
Metastatic	☐

Were they referred to a specialist? (Tick all which apply)

Resp. Physician	☐ if yes where _____
Thoracic surgeon	☐ if yes where _____
Oncologist	☐ if yes where _____
Not referred	☐

If they were **not** referred why was this?

Patient dying	☐
Severe co-morbid disease	☐
Patient request	☐
Not felt to be appropriate	☐

Did the patient receive any treatment? (Tick all that apply)

Surgery	☐ if yes where _____
Radiotherapy	☐ if yes where _____
Chemotherapy	☐ if yes where _____
No	☐

Any other relevant information

GpquestionnairepatientaliveVersion2

Dear Doctor,

Study – 'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

Re.

We are performing an audit of the management of all patients in Lothian, Borders and Fife diagnosed as having lung cancer in 2002. We will then compare this with a previous study performed in 1995. We shall be identifying all patients through the national cancer registration system, and have obtained permission from the Caldicott Guardians in the relevant NHS institutions to use patient identifiable data from this source for this purpose.

There are some patients, however, about whose management we do not have any information. The above patient was recorded by Cancer Registry as being registered with your practice at the time of diagnosis but according to mortality records has subsequently died.

We would be very grateful if, from your records, you could complete the enclosed questionnaire.

We appreciate that this may involve you in some time and trouble, but we are anxious to ensure as complete as picture as possible about the outcomes for patients with this very unfortunate diagnosis.

If you have any questions or require further information please get in touch with me at the address above.

Many thanks.

Yours sincerely

Dr Sara C. Erridge

on behalf of SCAN Lung Cancer Group

Gpletterpatientdeadversion1

Study – 'Lung cancer in Lothian, Borders and Fife: have treatment and survival improved since 1995?'

GP questionnaire Patient DEAD

Patients Name _____

Address _____

DOB ____/____/_____

Date cancer diagnosed ____/ _____/ _____

How was the diagnosis made?

Clinical	☐
CXR	☐
CT scan	☐
Bronchoscopy	☐
Other	_____

Was the cancer

Localised to the chest	☐
Metastatic	☐

Were they referred to a specialist? (Tick all which apply)

Resp. Physician	☐ if yes where _____
Thoracic surgeon	☐ if yes where _____
Oncologist	☐ if yes where _____
Not referred	☐

If they were **not** referred why was this?

Patient dying	☐
Severe co-morbid disease	☐
Patient request	☐
Not felt to be appropriate	☐

Did the patient receive any treatment? (Tick all that apply)

Surgery	☐ if yes where _____
Radiotherapy	☐ if yes where _____
Chemotherapy	☐ if yes where _____
No	☐

When did the patient die? ____/ ___/ ____

and what was the cause of death _____

Any other relevant information

Gpquestionniarepatientdeadversion1

Appendix 3: Combined stage analysis for 2002 and 2004 patients

The 2002 analysis suggested that there might be a difference in the stage at presentation between Fife and the other two health boards, but this was not statistically significant because of the smaller numbers in each group. Therefore a combined analysis of the 2002 and 2004 datasets was performed and is shown in the Table below.

Distribution of stage for patients with 'Not SCLC' within Lothian and Fife in 2002 and 2004

	Stage I	Stage II	Stage III	Stage IV	No detailed staging
Lothian (n=1033)	16.5%	7.5%	29.4%	35.7%	11.0%
Fife (n=833)	10.8%	6.5%	23.0%	48.9%	10.8%
BC 1995	24.0%		26.0%	37%	13%

The reasons for the variation in stage at presentation are difficult to determine. The proportion of patients undergoing bronchoscopy and pathological confirmation in 2002 was higher in Fife than Lothian, so the problem does not appear to be due to medical nihilism within the hospitals, but maybe with initial healthcare access. One study suggested that deprived patients with lung, breast or colorectal cancers are more likely to present as an emergency [150]. Though Fife has a much more socially deprived population than Lothian (see Table 6.2), there was no significant association with stage at presentation and deprivation in any of three cohorts in this thesis (Scotland 1995, BC 1995 and SCAN 2002) so it is unlikely that deprivation is the cause of the higher proportion of patients presenting with metastatic disease in Fife. The impact of social deprivation on stage at presentation has been extensively studied, with mixed results. In general, the association between more

advanced stage and social deprivation is weaker in patients with lung cancer, than has been observed in patients with breast and colorectal cancer [173, 209]. Bradley *et al* noted that in the USA, patients who were uninsured, but then enrolled on Medicaid when they were diagnosed with cancer, were three times more likely to have distant disease than those on Medicaid at time of diagnosis [23, 24].

Further prospective research is required to elicit the exact reasons for the observed differences in stage at presentation between the neighbouring healthboards in South East Scotland.

Appendix 4: Exploratory analysis of British Columbia 1995 and South East Scotland 2002

To investigate if the difference observed between Scotland and BC was due in part to inadequate staging of the Scottish patents in 1995, and to ascertain the impact of the increased use of potentially curative treatment a further exploratory analysis was performed comparing the BC patients diagnosed 1995 with the more recent cohort from South East Scotland.

The patient and tumour characteristics are shown in Table A4.1 Patients in Scotland were older and were less likely to have pathological confirmation. In both cohorts around 90% of patients had their stage of disease at presentation documented, but there definitely appeared to be a lower proportion of patients with localised, and hence the most curable, stage disease in Scotland. There also appeared to be more patients with involvement of the mediastinal lymph nodes.

Table A4.1Comparison of patient and tumour characteristics 1995 BC and 2002 Scotland

		BC 1995	SE Scotland 2002	
	Number	2073	971	
Gender	Male	1215 (59%)	537 (55%)	NS
Age	Median	68	71	**P<0.001**
	Range	22-96	37-94	(ANOVA)
Pathology	NSCLC	1540 (74%)	572 (59%)	**P<0.001**
	SCLC	306 (15%)	141 (14.5%)	
	no pathology	227 (11%)	258 (26.5%)	
	Localised	498 (24%)	132 (14%)	**P=0.001**
	Regional	538 (26%)	339 (35%)	
	Metastatic	756 (37%)	411 (42%)	
	Unknown	281 (14%)	89 (9%)	
	Potentially curative	546 (26.3%)	229 (23.6%)	P=0.08
	Palliative	826 (39.8%)	376 (38.7%)	
	No treatment	701 (33.8%)	366 (37.7%)	
	Resection	438 (21%)	102 (11%)	**P<0.001**
	Radiotherapy	836 (40%)	433 (45%)	**P=0.02**
	Chemotherapy	368 (18%)	196 (20%)	NS

The survival in SE Scotland (SCAN) remained inferior to that in British Columbia (adjusted HR death 0.88 (0.81-0.96), median survival of 7.3 v 5.1months log rank p<0.001). On Cox's regression analysis including the variable 'treatment intent' the hazard of death was reduced for patients in BC, women, patients aged under 70 years, with loco-regional disease, and with NSCLC pathology.

Patients treated with potentially curative therapy (PCT) also fared less well in SCAN (median not reached by 2 years in BC v 22 months SCAN log rank p=0.015). However, in BC in 1995 radical radiotherapy constituted only 20% of the PCT delivered, compared with 56% in Scotland in 2002 and radical radiotherapy even when combined with chemotherapy is a less effective treatment than surgery (figure A4.1). Of the patients with localised disease 56% underwent a resection in BC compared with 40% in Scotland (χ^2 p=0.006) When patients in South East Scotland were treated with the same modality of treatment they do not have inferior survival compared with patients in British Columbia (figure A4.1). Based on 40% five-year survival following surgery and 20% following radical radiotherapy for localised disease (based on actual 1995 BC and Scottish data) if the surgical rate in Scotland increased by 16% to 56% of localised cases and radical radiotherapy rate dropped from 32% to 16% then the percentage of patients with localised disease alive at five years could theoretically increase from 22% to 26%.

The difference seen in survival for patients treated with palliative treatment (median 6.3 in BC v 5.0months SCAN log rank p=0.001) was not associated with an increased adjusted hazard of death so the difference in age, pathology and stage were the main contributory factors for this group. However, for those patients receiving no treatment (median 2.6 v 1.5months log rank p<0.001) the difference remained (adjusted hazard of death 0.8 (0.7-0.9)).

This therefore suggests that the difference in survival seen between the two countries appeared to be due to

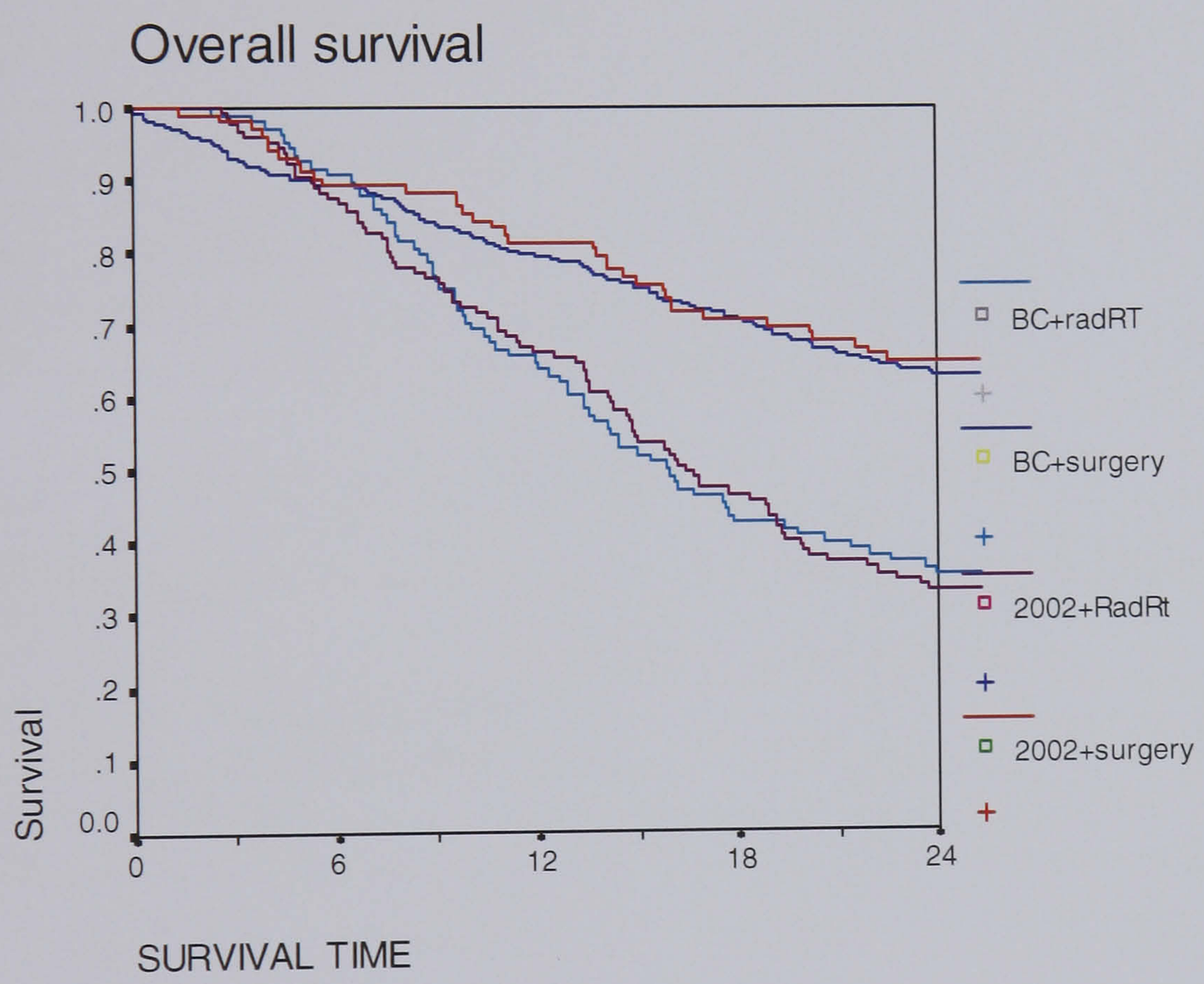
1) the older age

2) fewer patients with localised disease at presentation

3) less use of surgery for patients with localised disease

4) inferior survival of untreated patients.

Figure A4.1 Overall survival by treatment modality and year/country of diagnosis



$p<0.001$

Appendix 5: Summary of treatment delivered in South East Scotland in 2004

NSCLC		N=676
Surgery only	11.5%	77
Surgery and chemo	2%	16
Surgery, chemo and post-op radiotherapy	0.5%	2
Surgery and post-operative radiotherapy	1%	7
Surgery and palliative radiotherapy	1%	4
Radical radiotherapy	8%	56
Radical radiotherapy and chemo	7%	48
Palliative radiotherapy	23%	153
Palliative radiotherapy and chemo	4%	28
Chemotherapy	11%	75
None	31%	210

SCLC		N=163
Surgery only	1%	2
Surgery and chemo	1%	1
Chemotherapy	41%	67
Chemotherapy and adjuvant radiotherapy	20%	33
Chemotherapy and palliative radiotherapy	9%	14
Palliative radiotherapy	6%	10
None	22%	36

No pathology		N=214
Radical Radiotherapy	7%	14
Chemotherapy	1%	2
Palliative radiotherapy	14%	30
None	76%	168

Appendix 6: Estimate of resources required for optimal treatment of lung cancer

Based on the lower estimates of the models a rough calculation of the potential costs of initial treatment for every 1000 lung cancer patients was performed using NHS costs for 2005 taken from the English Department of Health website (Table A6.1).

Table A6.1 Potential costs of optimal treatment per 1000 patients

	Cost according to 2005 NHS charging		Number according 2004 data	Total cost based on 2004 data (£)	Number according 2002 data	Total cost based on 2002 data
Surgery	Complex thoracic surgery	£6540	118	771,720	119	778,260
Radical RT	CHART Stage I-II	37@ £238 + £80[1]	72	639,792	78	693,108
	33 daily fractions Stage III	34@ £142 + £80[1]	115	564,420	81	397,548
Post-op	20 daily fractions	21@ £142 +£80[1]	6	18,372	6	18,372
ChemoRT SCLC	25 twice daily fractions	26@ £238 +£80[1]	60	376,080	53	332,204
HD palliative chest	13 fractions	13@£105 +£80	17	24,565	12	17,340
Pall RT chest or brain	5 fractions	6@ £105	383	241,290	400	252,000
Pall RT bone	1 fraction	1@ £105	37	3,885	38	3,990
Chemotherapy NSCLC	4 cycles	4 @ £1072[2]	382[3]	1,638,016 (1,310,413)[4]	308[3]	1,320,704 (1,056,563)[4]
Chemotherapy L-SCLC	4 cycles	4@ £1072[2]	62	265,856 (245,917)	60	257,280 (234,125)
Chemotherapy E-SCLC	6 cycles	6 @ £1072[2]	75[3]	482,400 (393,960)[4]	63	405,216 (330,926)[4]
TOTAL				**5,026,396** (4,590,414)		**4,476,022** (4,114,436)

[1] includes additional visit for planning and £80 for radiotherapy planning CT scan

[2] Dept of Health website has conflicting costs of either £1072 per visit for chemotherapy for respiratory malignancy (D98) or £403 per visit for chemotherapy for NSCLC (X99LNS) and £141 for SCLC (X99LSC), but figure of £1072 per cycle seems more appropriate for currently used agents.

[3] over-estimate as <60% of patients actually receive all 4 cycles of chemotherapy

[4] revised costs based on 60% 4 cycles, 10% 3 cycles, 20% 2 cycles 10% 1 cycle (local audit results)

[5] revised costs based on 10% 1 cycle 10%, 90% 4 cycles (estimate of use in clinical practice)

[6] revised costs based on 10% 1cycle, 30% 4 cycles, 60% 6 cycles (estimate of use in clinical practice)

Table 7.11 Potential costs of diagnosis and staging of lung cancer

	Estimate of use	Total per 1000	Unit cost	
Diagnostic CT scan	90%	900	£160	144,000
Bronchoscopy	70%	700	£1059	741,300
CT guided biopsy	20% [112]	200	£160	32,000
PET for all potentially curative patients	31-28%	305-278	£884	245,752-269,620
CT brain Stage III for potentially curative therapy	12-8%	115-81	£160	12,960-18,400
TOTAL				1,160,012- 1,189,320

Other costs which have not been included are outpatient appointments (around £175 first visit and £100 thereafter), imaging to assess response to treatment, costs of any unscheduled in-patients admissions, transport costs and costs to the patient.

However, this does not include any costs of diagnostic and staging tests, which are outlined in Table 7.11. When these are included the total cost of diagnosis and initial treatment per 1000 lung patients diagnosed (who lived >1 day) is between £5.3 and 6.2 million.

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